DETERMINING RISKS TO HEALTH

Federal Policy and Practice

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Task Force on Health Risk Assessment

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FOREWORD

Risks to human health are pervasive. So, too, are needs to identify and measure those risks—to provide a basis for personal health decisions, to determine needs for governmental regulation, to monitor changes in our health and in things that affect our health, to set rational priorities for research, and for many other reasons. Thus, various parts of the U.S. federal government, and in particular the health agencies of the Department of Health and Human Services (DHHS), are deeply involved in the qualitative and quantitative assessment of health risks. These range from dioxin and cancer to smoking and heart disease; from explosions in grain elevators to the effects of orthopedic implants; from maternal alcoholism and birth defects to the release of recombinant DNA into the environment.

Despite this involvement, there has been little general appreciation of the scope and aggregate size of risk assessment activities, or of specific important features of the overall activity. We report here the first comprehensive DHHS-wide survey of activities related to the assessment of health risks, with descriptions of major programs, case studies, analysis of the findings, and suggestions about how mechanisms for risk assessments in general can be improved.

An assumption underlying the structure of this report is that any governmental effort to assess risks to the health of the American public must be held fully accountable to that public—in terms of the analytics, in terms of the processes applied in making a determination, and in terms of the ways a determination makes its way into policy. One of the unique features of this report is its side-by-side examination of risk assessments undertaken for regulatory purposes with those intended for use in public education (for example, heart disease risk for dietary fat) or for the delivery of medical services (for example, side effects attendant to a particular vaccine). A central premise of this approach is that most risk determinations, regardless of their stated intent, have a potential for substantial consequences in each of the domains of education, regulation, and service delivery.

This book should be of interest to many kinds of readers. Though it derives from the perceived need of policy officials in DHHS to have a clearer understanding of the processes and analytics used by DHHS agencies in drawing conclusions that are ultimately sent forward for policy decisions, its contents are more widely relevant. Persons involved in the legislative and regulatory machinery will learn something of how things work in practice, especially in areas outside their own programs. Those who do risk assessments, outside as well as inside the federal government, will learn about programs and processes, concepts and techniques that may help them do their work better. Students of governmental policy and management will learn about issues and solutions in a growing area of governmental activity that has rarely been studied and not even separately identified until quite recently. Persons in regulated industries and occupations will derive a broader view of regulatory concerns. Members of the general public, and those who represent the interests of consumers, will learn how important branches of government go about certain aspects of protecting human health and safety. The book in general can serve as a teaching text, a tool for general education, and a reference.

Chapter 1 outlines the background of this report and Chapter 2 introduces critical analytic terms and concepts, including a description of the key steps in any complete risk assessment. Chapters 3 through 8 present the descriptive results of the survey of DHHS efforts; 29 major program areas are discussed and 30 illustrative case studies are presented. Chapter 9 analyzes these descriptive findings by comparing the approaches of different programs, examining factors that lead to differences among programs, and outlining five kinds of issues that cut across program areas and individual hazards. Chapter 10 presents the recommendations of the Task Force on Health Risk Assessment about improving both the processes of risk assessment and the uses of the completed products.

Many loose ends remain. No other governmental agencies have examined their risk assessment activities in this way or in this depth; reports on other agencies would be valuable, and cross-agency comparisons more valuable still. The present report, as a pioneering effort, could not go into individual programs or issues in the depth that will be needed for follow-up studies. Our world is changing and the field of risk assessment itself is developing very rapidly; there will be a continuing need to both monitor new risks and develop new ways to assess risks.

The assessment of risks to human health is a critically important and scientifically challenging field. We all need to know more about it; here is a start.

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Chapter 1

INTRODUCTION

Risk is a reality of everyday living. Some risks are economic, others are social, still others are to our personal safety, national security, or enjoyment of our lifestyles and personal environments. Among these, risks to health and survival are widely perceived as the most pervasive and most vital. Day in and day out we confront myriad health risks from the environments we live in, the foods we eat, the modes of transportation we choose, the types of work we do, the building materials in our homes and offices, or the ways we spend our recreational time.

Various factors shape our attitudes toward these risks. For some of them, the risk may seem to be a small and necessary price to pay for things we want to do, or benefits we want to acquire. Certain of the risks are voluntary; others we cannot control. In some cases, the potential consequence is immediate; in others, years away. Some we take lightly; others we view with dread. Common to all of these risks is the fact that each affects our prospects for good health—for the long and happy lives we seek for ourselves and our families.

Determining just how these risks affect our prospects for health is a central mandate for the health agencies of government. If people are to act, individually or collectively, in a rational fashion to enhance their health prospects, they need the best available information about what constitutes a risk, the nature and magnitude of the risk, the strength of the evidence, and the various ways available to safeguard against adverse effects. It should be a primary responsibility of government at all levels to ensure the thorough and objective assessment of conditions offering potential harm to its public. Depending on the nature of the determination, it may then also be the responsibility of government to facilitate educational, service, or regulatory actions to help manage the risks.

Among agencies of the U.S. federal government, the Department of Health and Human Services (DHHS) has the broadest set of responsibilities for determining health risks. Though such determinations have claimed a relatively small share of the health dollars or personnel in DHHS—the bulk of agency resources going to delivery of health services to the underserved, to building the capacity of the nonfederal public health sector, to risk management efforts, and to research into basic biologic processes and the treatment of disease—increasing priority is placed on the DHHS mandate to apply the developing knowledge base in an integrative fashion to draw conclusions about health risks. Activities to this end span a very broad range, as illustrated by the work of the National Institutes of Health (NIH) to determine behavioral risk factors for cardiovascular disease and cancer; of the Centers for Disease Control (CDC) to determine the risk of toxic shock syndrome from the use of certain tampon products; of the Food and Drug Administration (FDA) to determine the risk of a nonnutritive sweetener proposed for addition to the nation's food supply; of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) to determine the risk of paraquat used to control marijuana crops; and of the National Center for Health Services Research (NCHSR) to determine the risks of new procedures for treating occluded coronary arteries.

The work of these and other agencies to determine various health risks holds substantial promise for improved understanding and control of the effects of health risks for Americans, but only if results are at once reliable and in a form that facilitates responsible risk management decisions either by a policy official or by the individual directly concerned. Regardless of whether the action taken is regulatory or advisory, the health, social, and economic stakes may be substantial.

Cognizant of both the risk management challenges confronting the DHHS with each new determination of a health risk and the many different ways in which the various DHHS agencies approach the conduct and reporting of their risk assessment efforts, in 1982 the Secretary of the DHHS requested a comprehensive review and analysis of department risk assessment activities. The review was to include recommendations for improving both the practices of DHHS agencies in arriving at determination about risk and the processes by which risk assessments are forwarded for policy decision.

The results of that review and analysis, accomplished through the participation of representatives from all agencies involved in making determinations about health risks, are presented here.

This review differs from other exercises examining activities in health risk assessment in two principal ways: (1) the scope is broader, going substantially beyond the estimation of the effects of toxic chemicals, to embrace all efforts within the DHHS to make formal determinations about health risks; and (2) a greater emphasis is placed on the processes by which determinations are formulated and forwarded for action at the policy level.

The administration, Congress, the public, and others have become increasingly interested in governmental health risk assessment activities, and many steps have been suggested for improving the practice of risk assessment. Though this broad interest is fairly recent, risk assessment is not a new governmental activity. Ample documentation exists for an appreciation of health risks throughout history, such as the hazards of eating contaminated food or of associating with persons who have contagious diseases. In the United States, the FDA and other regulatory agencies have been assessing the risks of exposure to potentially toxic chemicals for many decades.

The heightened interest in how the government reaches its decisions concerning potential health risks has resulted in large part from four recent changes: (1) increased requirements that agencies present explicit rationales for their conclusions and actions; (2) improved technology for identifying a greater range of the adverse health effects of various exposures and conditions; (3) better analytical methods for detecting hazardous substances in food, air, and other vehicles of exposure; and (4) new concepts of safety that are no longer based on "zero risk."

Several recent reviews of government risk assessment activities (OTA, 1981; NRC, 1982, 1983) have surveyed and discussed administrative processes and analytic procedures. Though these studies focus on cancer risk assessment, they have highlighted broader concerns and have suggested means to improve and maintain the integrity of risk assessment processes in government in general.

Another recent, broad government effort to examine and improve risk assessment includes the attempts of the Interagency Regulatory Liaison Group (IRLG) to develop guidelines for its member agencies to use in risk assessments for various adverse health effects. The first set of guidelines was developed for carcinogens (IRLG, 1979). The Interagency Risk Management Group (IRMG), a successor effort, was formed in early 1984. The IRMG, which consists of the heads of the Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), the Public Health Service (PHS), and the Occupational Safety and

Health Administration (OSHA), was formed to examine issues of mutual interest and concern, including generic issues related to the assessment of risks to the public health. Also in 1984, the EPA proposed revised guidelines for carcinogens and new guidelines for developmental toxicants, exposure assessments, and mutagens (EPA, 1984a, b, c, d). In late 1984, a Cabinet-level working group on health risk management was formed at the request of the White House. In support of this effort, in 1985 a report on risk management of toxic substances was forwarded to the Secretary of DHHS by the Executive Committee of the Committee to Coordinate Environmental and Related Programs (CCERP).

Risk assessment legislation introduced in both the 97th and 98th Congresses (97th: H.R. 638, H.R. 6159, S. 1442; 98th: H.R. 3840, S. 1983) addressed such issues as the organizational placement of risk assessment activities, the relationship between risk assessment and government decision making, and the development of standardized procedures for all federal risk assessments. The 97th Congress also appropriated funds for a review of federal risk assessment activities that was conducted by the National Academy of Sciences (NAS) and sponsored by the FDA (NRC, 1983). The report of that review addressed by the feasibility and value of governmentwide guidelines for conducting risk assessment recommended that such guidelines be developed for carcinogens, and suggested a procedure for their development. The Office of Science and Technology Policy (OSTP) has incorporated some of the National Research Council (NRC) suggestions in a revision of the IRLG approach to carcinogen policy for the federal regulatory agencies (OSTP, 1984). Appendix 5 presents in chart form a comparison of the risk-related definitions used by the NRC, by the CCERP, and in this book.

Concurrent activities in the DHHS have focused on strengthening data bases and increasing the technical capability of the department. Changes included the creation of the National Toxicology Program (NTP), the reorganization and growth of the CDC, and the development of databanks in various units of the DHHS such as the FDA's National Center for Toxicological Research (NCTR) and the National Institutes of Health's (NIH) National Library of Medicine (NLM).

The term "risk assessment" has in these efforts referred to a set of analytic procedures used to estimate the possible health effects of exposure to toxic chemicals. In many instances these analytic procedures are applied in a formal way in anticipation of possible regulatory action, but involvement of DHHS agencies in determinations of public health risk ranges far beyond the development of a scientific base for regulating exposure to one or another specific toxic substance, and includes a host of nonregulatory activities designed to eliminate or reduce exposure of the public to unnecessary risks associated with tobacco use, certain dietary patterns, alcohol consumption by pregnant women, illicit drug use, sedentary lifestyles, extremes of heat and cold, infectious agents, unneeded medical procedures, and a variety of other hazards. Despite the compelling demand for accurate, consistent, and reliable estimates of risk for all such conditions that may pose health hazards, the data and the analytic tools and procedures used in the efforts vary considerably from issue to issue, and many different mechanisms are used to present the findings.

These issues provide the backdrop for the preparation of this book. Chapter 2 presents the analytic terms and concepts, and Chapters 3 through 8 review the contributions to risk assessment of the following organizational units* of the DHHS: ADAMHA; CDC; FDA; NIH; and the Office of the Assistant Secretary for Health (OASH). Risk assessments used for decisions on reimbursement policies by the Health Care Financing Administration (HCFA) were also considered and determined to derive primarily from the other DHHS agencies mentioned above. (HCFA was fully represented on the task force.) Chapter 9 contains a comparative analysis of the various approaches to determining risk in the DHHS, by agency and issue. Recommendations are presented in Chapter 10. Appendix 1 is a list of abbreviations, and Appendix 2 is a glossary of terms used in this book. Appendix 3 lists references and resource documents. An organization chart of the Public Health Service is presented in Appendix 4. Appendices 5, 6, and 7 are, respectively, a comparison of component steps in health risk assessment; risk assessment and risk management of toxic substances; and a list of legislative authorities.

To provide a suitable framework for the analysis of procedural issues, information was collected on ten topics related to risk assessment activities: mandate, organizational placement, agenda or priority setting, risk assessment methods, scientific review, public involvement, description of risk assessment reports, mechanisms for forwarding results for policy decisions, procedures for disseminating findings to the public, and evaluation of public health impacts of assessments. Each of these topics is addressed explicitly in the discussion of individual programs. Also studied were specific cases in which DHHS agencies have engaged in

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*The term “unit” is used generically throughout to refer not only to the agencies listed above but also to their organizational components.

Exhibit 1–1 Nature of Risk in Case Studies from DHHS Units

Cases	*Nature of risk*	*DHHS unit*
Schizophrenia	inborn	ADAMHA
Lithium	chemical	ADAMHA
Fetal Alcohol Syndrome	behavioral-chemical	ADAMHA
Phencyclidine	behavioral-chemical	ADAMHA
Marijuana	behavioral-chemical	ADAMHA
Dioxin in soil	chemical	CDC
Aspirin-Reye Syndrome	chemical	CDC
Toxic Shock	behavioral-microbial	CDC
Swine flu	microbial	CDC
Pertussis	microbial	CDC
Ethylene dibromide	chemical	CDC
Styrene	chemical	CDC
Grain/feed mills	physical	CDC
D&C Green No. 6	behavioral-chemical	FDA
6-Methylcoumarin	chemical	FDA
Diethylstilbestrol (DES)	chemical	FDA
Moxalactam	chemical	FDA
Orthopedic implants	physical-chemical	FDA
Fat & cancer	behavioral-chemical	NIH
Fat & heart disease	behavioral-chemical	NIH
Radio-epi tables	physical	NIH
Cloning-Shiga	microbial	NIH
Mammography	physical	NIH
Analgesic-Kidney Disease	chemical	NIH
Liver transplant	physical	OASH
Percutaneous transluminal coronary angioplasty	physical	OASH
Lead exposure	chemical	OASH
Pentachloroethane	chemical	OASH
Ethylene dibromide	chemical	OASH
Passive smoking	chemical	OASH

Abbreviations: DHHS = Department of Health and Human Services; ADAMHA = Alcohol, Drug Abuse, and Mental Health Administration; CDC = Centers for Disease Control; FDA = Food and Drug Administration; NIH = National Institutes of Health; OASH = Office of the Assistant Secretary for Health.

efforts to determine the risks associated with various substances or conditions. These case studies focus on the scientific evidence used and on the judgments needed to reach a final risk determination.

The wide variety in cases studied and the nature of the relevant risks are noted in Exhibit 1–1. Each agency listed in Exhibit 1–1 engaged in the assessment and management of a variety of health risks, many of which have been of major concern to the public as well as to the Department and the health professions. Risk and risk assessments are often the subject of both news stories and legislative inquiry; examples from Exhibit 1–1 include phencyclidine (or "angel dust"), marijuana, dioxin in the soil at Times Beach, swine flu, diethylstilbestrol (DES), mammography, ethylene dibromide (EDB), and passive smoking. Risk assessment is largely a scientific and technical activity, but the choice of risks studied, the nature of the assessment process, and the way it is presented, perceived, and used all have major nonscientific implications. Thus our concerns go far beyond assuring that DHHS risk assessments are technically sound.

Chapter 2

ANALYTIC TERMS AND CONCEPTS

Chapter 2 presents key terms and concepts in the discussion of risk assessment activities. The framework is in part derived from the four-part approach of the National Research Council (NRC) Committee on the Institutional Means for Assessment of Risks to Public Health (1983). As noted previously, the health hazards of interest to the Department of Health and Human Services (DHHS) include not only chemicals but also many other sources such as those indicated in Exhibit 1–1 (Chapter 1). Because the principal focus of the NRC effort was on the assessment of toxic chemicals as carcinogens, the terminology has been adjusted to accommodate the much broader range of health risks considered here. We begin with the following definition of risk assessment:

> *Risk assessment is the qualitative or quantitative estimation of the likelihood of adverse effects from exposure to specified health hazards or from the absence of beneficial influences.*

The component activities of risk assessment are further defined according to the four types of analysis commonly required in any risk assessment:

- *Hazard identification:* the qualitative indication that a substance/condition may adversely affect human health;
- *Hazard characterization:* the qualitative and quantitative evaluation of the nature of the adverse effects, including their expression as functions of the amount of exposure (dose);
- *Exposure characterization:* the qualitative and quantitative evaluation of the degree of human exposure likely to occur; and
- *Risk determination:* the integration of these steps into a scientific determination of the level of risk as a basis for policy consideration.

Exhibit 2–1 compares the definitions of the NRC with those presented here. In the present approach, the first step (hazard identification) is the objective qualitative or quantitative determination of a potential hazard rather than a causal determination of risk; the second step (hazard characterization) embraces dose-response assessment, but also includes the determination of differences in risk across subpopulations as well as efforts to characterize by clinical or pharmacokinetic studies the action of the hazard; the third step (exposure characterization) is essentially identical to the NRC approach; and the fourth step (risk determination) ranges in nature from a binary (risk/no risk) conclusion to a formal, quantitative, multidimensional conclusion complete with sensitivity testing and detailed characterization of uncertainty. Thus, the model used here involves a step-wise approach proceeding from the first raising of suspicion to a formal quantitative determination of the risk attendant on some potential hazard.

Such conceptual differences make it necessary to consider the results of individual research studies undergirding risk determinations as important contributors to risk assessment more fully and more directly than do the NRC committee and other groups, which have in general chosen to note simply that research precedes risk assessment and provides the scientific basis for this

Exhibit 2–1 Comparison of Component Steps on Health Risk Assessment

NRC (1983)	*TFHRA (1985)*
Hazard identification: The determination of whether a particular chemical is or is not causally linked to particular health effects.	*Hazard identification:* The qualitative indication that a substance/condition may adversely affect human health.
Dose-response assessment: The determination of the relation between the magnitude of exposure and probability of occurrence of the health effects in question.	*Hazard characterization:* The qualitative and quantitative evaluation of the nature of the adverse effects, including their expression as functions of the amount of exposure (dose).
Exposure assessment: The determination of the extent of human exposure before or after application of regulatory controls.	*Exposure characterization:* The qualitative and quantitative evaluation of the degree of human exposure likely to occur.
Risk characterization: The description of the nature and often the magnitude of human risk, including attendant uncertainty.	*Risk determination:* The integration of these steps into a scientific determination of the level of risk as a basis for policy consideration.

Abbreviations: NRC = National Research Council, TFHRA = Task Force on Health Risk Assessment.

activity. While research is quite distinct from risk assessment, research results have a profound impact on each of the four steps of a complete risk assessment. Whatever data are available and relevant should be used in the development of a comprehensive statement about hazard identification, hazard characterization, and exposure characterization. Research findings tend to have a less visible, but even more profound, influence on risk determination because they go beyond data inputs to affect models, processes, and interpretations of results. Hence, though no recommendations are made (or intended) regarding the structure of the research process, methods of analysis pertinent to research studies are highlighted as indispensable sources of data required by risk assessors, particularly in the stages of hazard identification and hazard characterization.

The kinds of information commonly used in each of these four phases of risk assessment are illustrated in Exhibit 2-2, though the information is not meant to be comprehensive. Detailed discussions, including the strengths and weaknesses of various kinds of data, are available in several recent publications (e.g., Food Safety Council, 1979; OTA, 1981; NAS, 1982; OSTP, 1984), and a review of the central features of each step is offered below. Because the analytics involved in each of the four stages of risk assessment have been defined in greatest detail for application to the risks of toxic chemicals, a fuller discussion is presented for these procedures—particularly in the discussion of hazard characterization. However, the principles reviewed are applicable to the full range of risks covered here.

HAZARD IDENTIFICATION

Hazard identification addresses the first, often preliminary, indications that human exposure to some substance or condition may result in adverse health effects. This step of risk assessment is essentially qualitative. Potential endpoints of interest are diverse, ranging from minor infections, reversible physiological changes, transient central nervous system symptoms, and acute traumatic injury, to irreversible organ system damage, adverse reproductive outcomes, genetic alterations, cancer or other chronic disease, and death. Many effects, especially those of toxic chemicals, are not unique to a specific hazard, and occur in unexposed populations with some degree ("background rate") of frequency and severity. Thus, hazard identification must generally focus not simply on whether some outcome occurs, but on whether its frequency or severity is increased.

Exhibit 2–2 Information Used in Health Risk Assessment

I. Hazard identification
  A. Human data
    —Monitoring and surveillance (including vital statistics)
    —Epidemiologic studies
    —Clinical studies
  B. Animal data
  C. In vitro tests
  D. Molecular structure-activity relationships
II. Hazard characterization
  A. Human studies
    —Epidemiologic studies
    —Clinical studies
  B. Animal studies
    —Minimal effects determination
    —Dose-response modeling
    —Special issues, including interspecies conversion and high to low dose extrapolation
  C. Pharmacokinetic studies (including physiologic rationale)
III. Exposure characterization
  A. Demographic information
  B. Ecologic analyses
  C. Monitoring and surveillance systems
    —Animal
    —Human
  D. Biologic monitoring of high-risk individuals
  E. Transport modeling (mathematical)
  F. Integrated exposure assessments
    —Over time
    —Over hazard (synergy)
IV. Risk determination
  A. Mathematical
    —Unit and population risk estimates
    —Threshold determination (e.g., safety factor approach, NOEL)
    —Statistical characterization of uncertainty
  B. Formal decision analysis
  C. Inter-risk comparisons
  D. Qualitative—panel reviews
  E. Qualitative—informal scientific advice
  F. Risk-benefit analysis

Abbreviation: NOEL = no-observed-effect level.

For all types of risk assessment, the identification of possible exposure-related hazards tends to rely mainly on the results of clinical and epidemiologic studies and whole-animal experiments, although other types of scientific data, such as those from in vitro tests, can contribute to the identification process. Since clinical and epidemiologic studies deal directly with how humans do or do not respond to various agents and situations, they can be highly reliable indicators of potential human health hazards or, sometimes, the absence of hazard. Human data of adequate quality and quantity are rarely available, however, and results from whole-animal experiments may be used in lieu of, or to augment, epidemiologic data. Such experimentally derived data are often the primary or even the sole basis for making a determination of possible threat to human health.

Various types of in vitro screening procedures (Hollstein et al., 1979) have been developed for carcinogens and certain infectious agents, and other tests aimed at other effects are presently under development. Two of the short-term tests most commonly used to detect potential carcinogens are assays of mutagenic effects (Ames, 1979) and cellular transformations (NTP, 1979, 1980). Part of the current interest in these procedures stems from the qualitative correlation that has been reported (McCann, 1975) between the results of the Ames Test (an in vitro test of the capacity of a substance to produce mutations in the bacterium *Salmonella typhimurium*) and long-term cancer bioassay findings. In vitro tests are relatively inexpensive and short term, so they lend themselves readily to large-scale screening activities. However, methodological problems are still significant in application (e.g., the use of exogenous metabolic activation systems and interlaboratory variation in test results), and questions surrounding extrapolation of in vitro test results to humans have not been resolved.

Two assumptions provide conceptual basis for extrapolation from mutagenic effects in vitro to cancer in humans: (1) that since DNA is the hereditary material in all cellular organisms, a chemical producing mutations in one species is likely to do so in others, and (2) that cancer is in general a result of a mutation. However, species differ in their metabolism of toxicants, susceptibility to genetic alterations, and capacity to repair genetic damage (NRC, 1982). Experimental evidence supports extrapolation across species, in that chemicals that are mutagenic in one species are generally mutagenic in other species, but greater confidence is placed on qualitative than quantitative extrapolation.

A preliminary indication that a substance or condition may be a hazard to human health is sometimes inferred by comparing its critical characteristics to those of conditions known to be either hazardous or safe. For example, the toxicity of chemicals has been inferred from their structure and composition; the virulence of microorganisms has been inferred from their anatomic characteristics and nutrient requirements; the traumatic potential of physical agents such as radiation has been inferred from their physical properties; and preliminary inferences about the injurious potential of certain complex mixtures such as chewing tobacco have been made from their physical and chemical properties and what is known about their effects in other contexts.

Hazard identification by structure-activity relationships has been most commonly attempted in the case of potential carcinogens. Unfortunately, molecular structure is not highly predictive for this purpose, since carcinogens are known in a dozen or more chemical classes that share no common structural features, and each class also contains chemicals with no apparent carcinogenic activity (Miller and Miller, 1971; OTA, 1981).

Broad methodologic issues of hazard identification raise the following questions:

- How can the quality and relevance of individual studies be assessed?
- What relative weights should be given to studies with differing results? For example, should positive results outweigh negative results if the studies that yield them are otherwise similar? Should a negative study be weighted, at least roughly, in accord with its statistical power?
- How should evidence of different metabolic pathways or different metabolic rates between animals and humans be used in a risk assessment?
- How much weight should be placed on the results of various in vitro tests?
- What weight does similarity of chemical and physical properties add to the results of animal bioassays in the evaluation of risks for humans?
- How can the overall weight of the evidence in relation to hazard identification be best captured and expressed?

HAZARD CHARACTERIZATION

Hazard characterization concerns further evaluation of the evidence that a potential hazard causes an adverse health effect, and also with the relation between exposure (including dose, duration, and intensity) and the probability of various degrees of adverse health effects. Information for both activities may be derived from clinical, epidemiologic, animal, and/or pharmacokinetic studies.

Aside from controlled human clinical trials, the most meaningful human data for hazard characterization are positive epidemiological results that (1) are derived from a well-designed, well-executed study; (2) are unlikely to be due to chance variation (i.e., that are highly significant by appropriate statistical tests); (3) are reinforced by replication in a variety of settings; (4) show increasing frequency or severity of outcome with increasing dose; and (5) have exposure data of adequate quality. Negative epidemiologic studies can sometimes be used to place an upper bound on possible risk, but only if those studies are truly negative and if there are no other studies that present positive results from the same situation.

On the other hand, the epidemiological approach suffers from limitations that often inhibit its usefulness in the characterization of human health hazards. For example, the long latency period typical of many chronic disease endpoints makes it difficult to apply recent epidemiological information and complicates the design of retrospective studies, which must often depend on poor historical data. The sample size for an epidemiologic investigation is also frequently limited by costs or the availability of subjects, with the result that a particular study may have little sensitivity (i.e., statistical power) to detect health effects, even those that are common and severe enough to be of substantial concern. When positive results are observed, they may be confounded by the presence of other exposures or risk factors that are beyond the investigator's control and may not be amenable to full statistical adjustment or correction.

Even when epidemiologic results are available, they must often be supplemented with information from whole-animal experiments. Such experiments can be used to assess a wide variety of health-related outcomes of interest, both acute and chronic. Laboratory animals can be used to study a wide array of substances and conditions, such as microbes, chemicals, nutrients, and physical influences such as stress and trauma. Numerous tests for studying the effects of chemicals have been developed and codified (NRC, 1977b).

Hazard characterization often makes use of two general types of animal tests. Some tests, like the long-term carcinogenesis bioassay, are designed to identify diverse pathological responses in a wide variety of organisms (rat, mouse, hamster, guinea pig, rabbit, and nonhuman primates) and include acute, subchronic, and chronic (or lifetime) tests. These tests are generally used to identify target organs and estimate the likelihood that some dose of the substance will cause serious injury. Procedures also exist to characterize the pathogenicity of microbes. Other tests, like the teratogenesis screening assay, include methods of identifying specific forms of toxicity such as birth anomalies, reproductive dysfunction, mutation, skin sensitization, behavioral modification, and cancer. In addition to toxicity tests, there exist specific procedures to measure biotransformation and toxicokinetics of foreign substances in the host (NRC, 1977b; FDA, 1982).

Most scientists recognize the high degree of qualitative agreement between human risks and the findings of appropriate animal assays (NRC, 1977a). The strength of evidence from animal observations is enhanced if: (1) observed results are replicated in more than one sex, strain, species, or experimental setting; (2) greater exposure is associated with greater response; (3) the route of exposure and dosing regimen are similar to those encountered by humans; (4) the animal model is known to process (absorb, metabolize, detoxify, excrete, etc.) the substance under observation in the same manner as humans; and (5) the study sample size is large enough to ensure a high likelihood of detecting relevant effects.

Of particular importance in the estimation of human risks from experimental laboratory data are the consideration of species-specific factors that might cause differences in response between test animals and humans and the use of analytic procedures to accommodate those differences. Two general approaches have come to be used to characterize the relationship between the dose of a toxic entity and its effect: (1) the no-observed-effect-level safety factor (NOEL-SF) approach for substances that are thought to have a "threshold" dose for mediating adverse effects, and (2) the dose-response modeling approach for toxic endpoints for which it is assumed that no threshold dose exists.

The NOEL-SF approach draws from the basic principle that risk is a function of both the inherent toxicity or pathogenicity of a substance and the dose to which an individual is exposed. For most effects of most hazardous agents, there is a dose below which the effect will not ordinarily occur (i.e., a threshold). The highest dose at which no effect is detected in an animal study (the "no-observed-effect level," or NOEL) may approximate this threshold dose for the animal population under study. The NOEL in laboratory animals is taken as the starting point for estimating a dose unlikely to elicit adverse effects in humans. Estimates of safe levels are usually derived from NOELs by the application of safety or uncertainty factors. An alternative closely related to safety factors is the margin of safety (MOS), in which the ratio of NOEL to actual exposure is calculated and a qualitative judgment is made about whether that ratio provides adequate protection.

A sharper alternative to the NOEL-SF approach is the application of mathematical models to experimental (sometimes human) data to extend the dose-response curve and to estimate health risks at one or more exposure levels. This mathematical dose-response modeling approach has been particularly emphasized in the area of carcinogenesis but could in theory be applied to other health risks (e.g., bone marrow depression with exposure to benzene, or effects of toxins on enzyme levels in the blood).

Carcinogenic effects, in contrast to other toxic endpoints, are thought to have no threshold and to be induced proportionately at all relatively low dose levels; thus the general principle that the probability of a toxic manifestation is likely to increase with increasing dose still holds for carcinogens. In almost all cases, however, the region of concern about human exposures to environmental carcinogens is at doses very much lower than those used in laboratory experimentation. Exposures used in animal studies of carcinogenicity often approximate the maximum dose that the test animal can tolerate (maximum tolerated dose or MTD) because of the need to minimize cost and maximize logistic control of studies. Whether the approximate linearity of response holds throughout the range from the dose of concern in human exposure to the MTD in laboratory experiments is unknown.

Mathematical models of the relation between dose and response can be used to estimate the probability of a response (e.g., cancer) at doses not included in an animal study. Furthermore, the analysis usually must accommodate some "natural" or "background" frequency or severity of the condition that occurs as a result of genetic disposition or exposures to other substances. Mathematical models make use of high dose/high incidence data to provide the policy maker with a possible upper bound on risks at lower (ambient) human doses (NRC, 1983). For example, if a group of 50 animals is exposed to a dose of a carcinogen and six develop cancers, in contrast to one cancer in a group of 50 controls, then the additional number of animals affected by this dose is 5, or 10 percent. An increase of this size is about the smallest that can be detected reliably in most animal experiments of practicable size (OTA, 1981), though lifetime human risks of one per hundred thousand or one per million may be of concern in public health policy.

While the experimentally derived relationship between dose and incidence is the starting point for assessment of carcinogenic risk, accuracy of the projected risk cannot be determined empirically. Thus, application of extrapolation models introduces uncertainty into the risk assessment. The models now in vogue to predict cancer risks at low doses are based on general theories of carcinogenesis and include the one-hit and the multistage models. Other models for risk assessment (e.g., the multihit, the probit, the Weibull, and the logit) have had limited use.

Of these, one can show mathematically that the one-hit model yields the highest estimate of low-dose risk. It is based on the biological theory that a single "hit" at a cellular target (DNA) by some minimum critical amount of hazard initiates an irreversible series of events that eventually leads to a tumor. The model thus predicts that the effect is directly (linearly) proportional to the dose applied, no matter how small. Thus, if the probability of cancer at low doses is in fact higher than predicted by the one-hit model, risks will necessarily be underestimated.

The multistage model is based on the same general theory of cancer initiation as the one-hit model, but it postulates that a specific carcinogen may affect more than one stage in the sequence of development of a cancer. In its original form, this model is limited because at low doses it cannot show risks higher than those derived from the linear model. However, the multistage model does accommodate substances that are initiators (primary stage carcinogens), promoters (late stage carcinogens), or both. As a result the low-dose risk estimates are consistent with a broad class of plausible carcinogenic mechanisms or responses (Crump et al., 1976; NRC, 1977b). Some observers believe that the multistage model is a truer reflection of the chemical carcinogenesis process and therefore has a stronger scientific rationale.

"Tolerance distribution," of which the probit model is the best known, assumes that each individual in a study population has some threshold level such that higher doses cause cancer and lower doses do not, and that though these thresholds vary from individual to individual, they can be described in terms of a probability distribution function. One of the first low-dose extrapolation procedures to be used in carcinogenic risk estimation, the Mantel-Bryan procedure (Mantel and Byran, 1961), is based on the probit model. While it was originally thought to be a conservative approach to risk estimation, subsequent findings (Hoel et al., 1975) indicate that in practice it produces substantially lower estimates of risk, and higher estimates of virtually safe doses, than other extrapolation procedures; it is now seldom used.

The risks estimated by extrapolation techniques apply directly only to the populations of animals tested. When human health risk estimations are based on laboratory animal data, the doses must be converted to equivalent doses in humans. This interspecies conversion is complex and a source of substantial uncertainty because of the many species-specific physiologic, metabolic, and genetic factors that may cause the responses of the test animal to differ from those of humans. Moreover, the three mathematical models can arrive at substantially different estimates of risk based on the same data. For example, in estimating from rat data the human risk for cancer from saccharin consumption at a dietary intake corresponding to 0.12 g/day, the results from different models range from 0.0034 percent to 0.1 percent, a 300-fold difference (NRC, 1978). Additional complexities arise with attempts to assess mutagenesis and teratogenesis of substances based on interspecies conversion.

Hazard characterization is at once a critical and complicated stage of risk assessment. With all of the potential for errors due to the vast differences among humans, and between humans and test animals, in biology, population heterogeneity, exposure modes, and secondary environmental conditions, conclusions must be drawn carefully and take full accounting of the critical assumptions and salient uncertainties. During this stage of the analysis the following issues must be dealt with fully and directly:

- Under what circumstances should one or another dose-response model be used to extrapolate from observed doses to relevant doses?
- Should dose-response relations be extrapolated according to best estimates, according to upper confidence limits, or by some other rule?
- How should one deal with different temporal exposure patterns in the study population and in the population for which risk estimates are required? For example, should one assume that lifetime risk is only a function of total dose, irrespective of whether the dose was received in early childhood or in old age? Should recent doses be weighted less or more than earlier doses? How should doses be considered for either agents that propagate or effects that propagate?
- What factors should be used for inter-species conversion of dose from animals to humans? Should different factors be used for different categories of risks?
- How should the risk assessment use information on differences between experimental animals and humans in metabolic processes and rates in defense mechanisms and repair procedures?
- If data are available on more than one nonhuman species or genetic strain, how should they be used? Should only data on the most sensitive species or strain be used to derive a dose-response function, or should the data be combined? If data on different species and strains are to be combined, how should this be done?
- How should data from retrospective studies be extrapolated to present or future exposures?
- How credible is the biologic explanation for the effect?

EXPOSURE CHARACTERIZATION

Exposure characterization focuses on the number of people exposed and their patterns of exposure. A complete description of exposure patterns should include, at a minimum, route, dose, frequency, duration, and timing of exposure. Exposure characterization also includes descriptive features of the exposed population and its components, expecially the determination of any characteristics that would place an individual at increased risk of an adverse health effect due to exposure.

Attempts are sometimes made to relate the effects of behavioral risk factors, (e.g., smoking cigarettes during pregnancy) to other risk profiles in the same populations (e.g., birth weight of offspring). In some unusual circumstances, assessment of a hazard may be divided into the separate issues of exposure to and the effects of its various components. Since, for example, consumption of convenience foods may raise several nutritional issues, their composition and effects may be examined separately by class of lipids and the ratios in which they are ingested, or perhaps by gross measures of fats, carbohydrates, proteins, and salt. Similarly, the effects of cigarette smoke may be subdivided into the effects of nicotine, tar, carbon monoxide, and other components.

The tools for exposure evaluations have recently improved with the perfection of personal monitoring devices, the study of microcosms, and the development of sophisticated mathematical exposure models. Concentrations of a toxic agent in the environment may be measured at various locations and various times to determine average exposures and depletion patterns. For substances in the workplace, it is sometimes possible to estimate exposure (as well as effects) by physical examination or biological monitoring of exposed employees, as in the measurement of blood lead levels, or of chromosomal changes which, while not definitive measures of exposure, may offer an early warning. Simulation is often based on either the study of microcosms (a minienvironment created in the laboratory) or mathematical modeling. Modeling has been extensively used for air pollutants by estimating air concentrations from known smokestack discharges in various areas, and then making assumptions about the relation between air concentrations and inhaled doses.

Characterization of the population groups likely to be exposed to a risk may also be an important consideration in exposure assessment, expecially in situations where such characteristics as age, pregnancy, or concurrent disease may place individuals or subpopulations at above-average risk of adverse health effects. Typical high-risk individuals would be asthmatics exposed to airborne toxic chemicals, cigarette smokers exposed to asbestos, a fetus exposed to methylmercury, or the elderly exposed to influenza.

Exposure to a lifestyle risk is often characterized by data from surveys establishing the prevalence of behavioral risks for given population groups. Demographic, socioeconomic, and other factors may be analyzed to determine specific characteristics of high-risk individuals of groups. Monitoring and surveillance systems often produce information for exposure assessments, even though such are not specifically designed as risk assessment studies.

The lack of reliable data on exposure is too often the point of greatest vulnerability in the risk assessment process. There frequently seems to be a much greater uncertainty in estimates of actual or anticipated exposures than in the potential effects of exposure to a particular level. For whatever reasons—a lack of appeal as a scientific question, a zero risk philosophy that makes magnitude of exposure a moot point, a failure to appreciate how exposure data are critical in risk assessments as well as risk management—little is known about true patterns of exposure to many hazards. The concentration of a substance in air or soil may be known, for example, but there is little indication of who is exposed, by what routes, for what duration, and at which end of the concentration gradient. When such detailed knowledge exists, there may remain uncertainty because the patterns of human activity create numerous exceptions to the norm.

The exposure assessment phase requires careful resolution of issues such as the following:

- How should one predict atmospheric dispersion of substances in light of vertical convection, wind currents, etc., or predict seepage rates of toxic chemicals into soils and groundwater?
- Should point estimates or a distribution be used?
- How should differences in timing, duration, and age at first exposure be estimated?
- What is the proper unit of dose for chemicals? For microbes? For physical agents?
- How should one estimate the size and nature of the populations likely to be exposed?
- How should exposures of special risk groups, such as pregnant women and young children, be estimated?

RISK DETERMINATION

Risk determination is the overall conclusion about the likelihood of disease or injury and the magnitude or severity of effects that would attend exposure. It involves a synthesis of the information from the hazard identification, hazard characterization, and exposure characterization steps. The result of this synthesis may be expressed only as a qualitative statement of risk, or it may include quantitative statements. A full risk determination also points out the scientific uncertainties in the assessment. Risk determinations may be derived from subjective (though formal) panel deliberations, simple risk-risk comparisons, or the use of some generally accepted quantitative model.

Several examples of the latter are instructive. For threshold effects, models focus on the integration of quantitative risk information with estimated human exposures to ascertain whether risks are acceptable or not. For nonthreshold effects, allowable exposures are generally developed from a populationwide, dose-response curve to assure that risks do not exceed some specific level (e.g., a risk of one per million exposed persons over a lifetime). The integration step also includes a summary of qualitative data on the strength of the association between exposure and adverse effect.

As noted earlier in the discussion of hazard characterization, a common approach to the estimation of chemical and physical risk for reversible toxic effects with thresholds, or equivalently, to the determination of "safe" or "acceptable" levels of human exposure, has been to apply safety (or uncertainty) factors. In this approach, a NOEL determined by tests in experimental animals is divided by an appropriate safety or uncertainty factor to obtain an "acceptable" or "safe" dose for humans. A safety factor of 100 is common (sometimes justified as reflecting a worst-case, order-of-magnitude increase in sensitivity in humans above laboratory animals, and a further order-of-magnitude variability of response within the human population). For carcinogens, a third order-of-magnitude is sometimes used to reflect the severity of the effect, giving a safety factor of 1,000. Factors ranging from 10 to 1,000 (Dourson and Stara, 1983) have been proposed depending on the nature of the health endpoint under consideration and the quality of the experimental data.

For microbial risks, a conceptually similar approach is used to identify the exposure conditions at and below which infectivity (and disease) are not manifest. However, formal safety factors are not normally used in the application of risk findings to the issue of human exposure to microbes.

The NOEL-SF approach, while relatively easy to apply, has several limitations. It is dependent on experimental sample size (at any given dose level, a specific adverse effect is less likely to be detected in a small experiment than a large one). Furthermore, it gives no consideration to the shape of the underlying dose-response curve, even though a shallow slope would seem more likely to elicit concern than a steep slope in the neighborhood of the measured NOEL. Finally, its usual justification implies the questionable assumption of the existence of a true threshold below which humans do not respond, or at least do not respond with a frequency or degree that is of concern to the risk assessor.

When science does not provide a definitive answer in a risk assessment, professional judgment and policy considerations must enter the process. The judgments that are required to make a final risk determination and the way in which expressions of risk are communicated to policy makers have been major causes of concern for critics of risk assessment methods used by governmental agencies. The uncertainties of the scientific basis for risk assessment must be addressed explicitly and in detail in the final, integrative step of risk assessment.

Information can be assimilated and synthesized by any of several processes (e.g., consensus development conferences, National Institute for Occupational Safety and Health (NIOSH) criteria documents, state-of-the-art conferences), all of which rely on weighing all of the evidence in terms of experimental design, reproducibility, and concordance across several species.

This assimilation and integration can be undertaken by a single staff analyst in the normal course of workday events, or by an assembly of eminent scientists with diverse but relevant technical backgrounds, or by researchers with any intermediate combination of numbers, breadth of expertise, and professional standing. Ideally, the conclusion derived from the assimilation and integration will express the nature and extent of the cause-effect relation between the hazard under analysis, its effects on diseases and physiologic alterations of concern, and the level of uncertainty attendant to the analysis.

Uncertainty in risk assessment arises from two fundamental sources: (1) missing or ambiguous information about a particular substance, and (2) gaps in current scientific theory. When the risk assessment team finds that such information is missing and needed, a decision is required before the analysis can proceed. For example:

- Should a best guess be made about the missing information?
- Should another kind of analysis be undertaken to side-step the gap?
- Should the analyst try to "bracket" the uncertainty by two or more related estimates?

- Should the agency simply establish and follow some policy on the matter?

Choices made at these decision points must be highly informed by current scientific thought and must be fully documented in the analysis. Though a risk assessment may require many decisions for which there is no clear scientific consensus about the best choice, the analysis can proceed with appropriate understanding and conveyance of the existing uncertainties.

The uncertainty pervasive in the risk assessment process has been a major problem for regulators who depend on risk assessment as an essential analytic tool for setting public policy. The existence of uncertainty means that determinations of risk must be stated in qualifying language that highlights their lack of precision. The inability to produce a single, precise figure for the risk of a substance thus invites concerned parties to criticize the scientific basis for a policy decision with which they disagree. Many issues of public policy, however, cannot wait until the gaps in scientific knowledge have been completely filled and risk estimates are more certain, but decisions must be made in carefully structured processes using the best information available.

Some observers distinguish between risk determinations made for regulatory purposes, such as those of the Food and Drug Administration (FDA) and the NIOSH, and those made for other health purposes, such as those of National Institutes of Health (NIH) for public advisory and education or service delivery. Clearly, regulatory and nonregulatory risk assessments differ in such things as the nature and specificity of legal and regulatory mandates, the deliberateness with which the analyses are structured, the degree of openness of the process, review and clearance procedures, and the type and specificity of reports issued.

In particular, when a risk assessment is to be used for regulatory purposes, the studies for, and conduct of, the first three stages are driven rather directly by the nature of the regulatory challenge; for nonregulatory risk assessments, the analytic inputs for these stages are derived less formally from the large body of investigator-initiated research. To the extent that such differences exist, they seem natural and appropriate features of their respective processes.

These distinctions begin to blur, however, in the integrative phase: the actual risk determination. A risk determination for a certain pesticide may inherently be no more economically consequential, no more socially relevant, and no more broadly applicable than a determination about the risks attendant on dietary fat intake or a determination of risk attendant on exposure to a new strain of vaccine-preventable influenza. A determination made for nonregulatory purposes (e.g., tobacco hazards) may have regulatory consequences (e.g., labeling policy), and a determination made for regulatory purposes (e.g., drug safety) may have nonregulatory consequences (e.g., treatment and reimbursement programs). Whatever the reason behind the development of a given risk determination, its implications and ultimate uses can be broad.

Beneath the differences, therefore, a broad and substantial unity reflects the roots of both regulatory and nonregulatory risk determinations in the objective assessment of relevant data against technically based criteria, and the interpretation of those data in light of current understanding of relevant science. A complete risk assessment of any type involves each of the four steps presented in this chapter. Because of the fundamental unity of social application, all assessments culminating in a determination of health risk are treated together.

Chapter 3

ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) is the focus for the federal effort to increase knowledge and promote effective strategies to deal with problems and issues associated with the use and abuse of alcohol and drugs, and with mental illness and mental health. Assessments of the health risks associated with mental illness and its treatment and with alcohol and drug use are an important component of ADAMHA's activities and are conducted by all three ADAMHA institutes: the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Institute on Drug Abuse (NIDA). The Agency Overview section of this chapter presents the general procedures and policies related to the conduct of risk assessment in these institutes, while the case studies that follow highlight analytic processes characteristic of risk assessments conducted within ADAMHA.

AGENCY OVERVIEW

Risks Associated with Mental Disorders: NIMH

The National Institute of Mental Health (NIMH) is responsible for research to identify and characterize risk factors in the occurrence and treatment of mental disorders. Research results are periodically evaluated and communicated to scientists, mental health professionals, and the public.

Mandate

Created by the National Mental Health Act in 1946, the NIMH provides leadership, policies, and goals for the federal effort in the promotion of mental health, the prevention and treatment of mental illness, and the rehabilitation of affected individuals. Section 301 of the Public Health Service Act authorizes current activities in research on the (1) etiology, prevention, diagnosis, and treatment of mental health disorders; (2) collection of data on the extent of and national responses to mental health problems; (3) provision of technical assistance to other federal, state, local, and private prevention and treatment organizations; and (4) technology transfer to scientists, professionals, and the public concerning research findings and mental health programs.

Organizational Placement

The NIMH is composed of three extramural research divisions—the Division of Extramural Research Programs, the Division of Prevention and Special Mental Health Programs, and the Division of Biometry and Epidemiology—and one intramural research division. It also includes a service-system-improvement demonstration program—the Office of State and Community Liaison—and a Division of Communication and Education.

The Division of Extramural Research is responsible for a wide variety of etiologic factor research, including basic studies of the brain, behavior, schizophrenic disorders, depression and manic-depressive illness, mental disorders of aging, childhood disorders, anxiety disorders, and stress and psychosomatic disorders. Of its branches that support research on risk factors contributing to the development of mental illness, the Pharmacologic and Somatic Treatments Branch and the Psychosocial Treatments Research Branch are primarily responsible for research on the efficacy and associated risks of treatments. The Clinical Research Branch focuses on research on the assessment, diagnosis, and etiology of mental disorders, while the Neuroscience and Behavioral Sciences Research Branches focus on studies on the biology of brain and behavior and the bases for normal and abnormal behavior. The Division of Intramural Research Programs conducts studies in similar areas.

The Division of Prevention and Special Mental Health Programs supports a number of research projects undertaking secondary analyses of existing longitudinal data sets on children and adolescents in order to identify modifiable risk factors. Hopes are that such efforts will lead to the development of preventive interventions targeted to these populations. In addition, the division supports research projects to identify risk factors associated with the development of antisocial and violent behavior in adolescents, depression in women, failure-to-thrive syndromes in infants, cognitive and emotional deterioration in the elderly, and emotional dysfunction in chronically, physically ill children and adults.

The Division of Biometry and Epidemiology has the primary responsibility for epidemiological studies supported by the NIMH. Within this division, the activities of the Epidemiologic Catchment Area (ECA) program are most directly related to risk factor research.

Agenda Setting

Research planning and evaluation are coordinated in the Office of Policy Development, Planning, and Evaluation in a three-year process that is reviewed annually. Research planning at the NIMH is a function of input from intramural and extramural investigators, staff, the National Advisory Mental Health Council, the public, and Congress. State-of-the-art conferences assess research needs in specific areas.

In the extramural research program, conferences and workshops lay the groundwork for the development of requests for research applications (RFAs). Grant applications for extramural research are reviewed by one of the four review branches—Basic Research, Clinical and Services Projects, Research Development, and Applied and Special Projects of the Office of Extramural Project Review, a separate office within the institute. They are then assigned to one of the committees within each branch for review. These committees review applications for scientific merit; for significance of topic in promoting clarification of mental health issues; especially in understanding disease processes and treatment applications; and for qualifications of researchers. By law, all applications must be reviewed and approved by the NAMHC before they can be funded.

The research agenda of the Intramural Research Division is determined by the institute's scientific director, who, in consultation with the board of scientific counselors, allocates funding support to selected research projects. The board of scientific counselors consists of several permanent members, appointed for fixed terms, who participate in all reviews, and of ad hoc members retained for review of grant applications in specific research areas. Generally, Intramural Laboratory directors consult with associate directors of research, who present requests for funding to the board. Board recommendations are reviewed by the scientific director, who makes the final decision on all research allocations.

Since scientific progress is often unexpected and unplanned, the continued preeminence of intramural research depends on the ability of individual scientists to recognize and pursue fruitful opportunities as they arise. Intramural researchers are aided in this mission by a unique environment, characterized by the stability of resources, which enables intramural scientists to make a career of investigative work and to undertake long-term projects that might be regarded as too economically risky in a grant-supported university setting.

Risk Assessment Methods

Health risk assessment activities in the NIMH extend from the routine collection of statistics on the use of mental health services to laboratory studies of biochemical and physiological risk factors. Although the measurement of disease prevalence and incidence is advancing rapidly with the development of new diagnostic instruments, specific risk factor studies and longitudinal studies of individuals presumed to be at high risk are still in the early stages.

Risks Associated with the Occurrence of Mental Disorders. The NIMH conducts a national reporting program on the use of mental health services in the United States, including surveys of correlations between patient sociodemographic variables and use of services. To the extent that these variables are risk indicators for illness, they may set a broad framework for more specific risk factor studies of mental disorders. The largest current population-based epidemiologic study of mental disorders, the ECA program, is a collaborative effort of the NIMH Division of Biometry and Epidemiology with five universities across the country. The ECA is designed to apply the best diagnostic screening methods to household and institutional samples in five areas. The first of two sets of surveys will observe the distribution of disorders according to demographic variables such as age, sex, and race, while a set of follow-up surveys will measure the incidence of new disease in the same subjects, testing risk factors that may predict new cases. In addition to the ECA study, a special announcement is being issued to stimulate epidemiological investigations of risk factors for specific disorders.

Biochemical and physiological abnormalities that may be genetically related to mental illness are being studied in the Intramural Research Program and by numerous academic scientists on extramural research grants. Most of the studies begin with abnormal findings in mental patients and then attempt to extend observations to offspring or relatives of patients or to population samples. Since offspring or relatives of patients are generally more likely to be vulnerable to mental disorder, familial factors predisposing to mental disorder have been extensively studied. An investigation of schizophrenia in adopted children of schizophrenics, for example, have reinforced evidence for biological inheritance. The institute also sponsors studies designed to detect childhood manifestations of vulnerability to schizophrenia. Most of this research is based on children of schizophrenics. Although there is a growing portfolio on affective disorders in offspring and relatives of patients with affective disorders, it is still at too early a stage to assess degrees of risk. Among children of schizophrenic parents, at least 10 percent of whom will develop schizophrenia, research seeks to identify early biochemical, physiological, or life-history characteristics that differentiate those who will ultimately develop schizophrenia from those who will not. Other studies focus on disturbed adolescents from families with deviant interpersonal interactions to assess risks for a broad range of maladaptive behaviors or mental disorders.

Risks Associated with Treatment of Mental Disorders. Risks associated with treatment of mental disorders are identified and characterized through NIMH-sponsored clinical studies of the safety and effectiveness of such treatments. In general, a drug under consideration for use in the treatment of mental disorders is evaluated using clinical trial methodology and the staging prescribed by the Food and Drug Administration (FDA) investigative new drug process (see Chapter 6). After preclinical testing, normally consisting of pharmacology, acute toxicity, and subchronic toxicity studies, clinical studies are conducted in several phases, beginning with small-scale controlled studies and followed by more extensive trials with larger numbers of subjects. In such studies, acute and chronic toxicity and side effects are reported along with information on clinical effectiveness. An important consideration in the overall evaluation of the usefulness of the drug is a comparison of the drug's risk/benefit ratio to risk/benefit ratios for other drugs used to treat the disorder being evaluated. Recent advances in clinical assessment and research methodology, such as the use of treatment manuals, have made it possible to assess the safety and efficacy of specific psychosocial treatments with specific disorders.

The Division of Extramural Research Programs also sponsors consensus development conferences to assess the safety and efficacy of various treatments (see Chapter 7). In such cases, studies at the NIMH and other institutions are evaluated by an independent panel of experts who make a determination of the safety and efficacy of a treatment.

Risk Associated with System Responsiveness to the Mentally Ill. The NIMH Office of State and Community Liaison, in collaboration with state mental health authorities, conducts two national demonstration projects designed to apply the best systems' improvement technology and practices to selected state mental health systems. The Community Support Program (CSP), with projects in all 50 states, has demonstrated the efficacy of internal advocacy, system change technology, and statewide systems improvement for the chronically mentally ill. The recently initiated Child and Adolescent Service System Demonstration Project (CASSDP), while adopting many of the principles of the CSP, will develop new technologies and practices for improving and coordinating mental health services for severely emotionally disturbed children and adolescents.

Scientific Review

Review mechanisms for research reports within the Intramural Division of the NIMH are similar to those elsewhere in the ADAMHA and in the National Institutes of Health (NIH). In addition to annual reviews of research progress, the NIMH has initiated project officer reviews, in which project officers produce a report assessing the body of findings in a research area. Results of project officer reviews are presented at review conferences; final reports of research projects are submitted to peer-reviewed journals.

Branch chiefs review progress reports on extramural research projects. In addition, a research advisory group to the director, consisting of all division directors and a rotating group of branch chiefs, meets weekly to review special research areas.

Public Involvement

The public can become involved in NIMH health risk assessment activities by attending NIMH-sponsored conferences and through public representation on the institute's Advisory Council.

Description of Risk Assessment Reports

Results of intramural and extramural assessments are generally published in peer-review professional journals. NIMH staff also issue the following in-house manuals and periodicals:

- *Risk Factor Research in the Major Mental Health Disorders,* a monograph summarizing the status of risk factor research in 1980.
- *The Schizophrenia Bulletin,* a quarterly publication of the Center for Studies of Schizophrenia that facilitates dissemination and exchanges of information about schizophrenia and it provides a forum for informed scientific discussions about recent advances and controversial topics in schizophrenia research.
- *The Psychopharmacology Bulletin,* a publication with approximately 3,000 subscribers worldwide that rapidly disseminates research findings in psychopharmacology generally inaccessible or unavailable from other sources. It attempts to bring findings and issues of public health importance to the attention of scientists and clinicians.

The Division of Communication and Education, in conjunction with the Intramural and Extramural Research Programs, disseminates information generated through NIMH research programs to the public and press, and responds to many thousands of requests for information each year. The NIMH regularly updates publications used to answer these requests and adds new publications as necessary to handle the accumulation of research information.

The Office of State and Community Liaison disseminates information generated through the NIMH service systems improvement demonstration programs to state and local mental health systems managers, providers, policy makers, and advocates.

Mechanisms for Forwarding Results for Policy Decisions

NIMH health risk assessment activities are used in determining research priorities at the NIMH and other federal research agencies, in information dissemination activities within the institute, and in policy decisions about the regulatory approval of treatments by the FDA. The NIMH does not make policy relating to the safety and efficacy of treatments, but makes formal written and informal verbal recommendations to the FDA and other government agencies concerning treatments. If significant and previously unrecognized risks of new or preexisting treatment are identified through either research or clinical application, the investigator/clinician must file a special Adverse Effects Report with the FDA.

Research priorities within the institute are influenced by findings that implicate various factors as increasing or decreasing the risk of mental disorders and by findings of significant effects of treatments. Information dissemination decisions rest ultimately with the institute director and follow an institute review of research results.

Procedures for Disseminating Findings to the Public

Peer-reviewed journals convey most research findings to professionals, but the Division of Communications and Education has primary responsibility for dissemination of information from the NIMH to the lay public. The division also produces several publications for use by the research and professional communities, including *Science Reports* (case studies of NIMH-supported research and its significance), *Science Monographs* (state-of-the-art reviews on selected topics), and annotated bibliographies of books and articles derived from the NIMH computer data retrieval system.

Materials to the public include general health advisories, information pamphlets, educational materials for use in schools, and posters or flyers. The division may also integrate these materials into media campaigns, using several dissemination "keys," including the press and other major media, colleges and universities, community mental health centers, and occasionally even marketplaces such as grocery or drug stores. Speeches and public education seminars by Intramural and Extramural staff provide a further means of dissemination.

In compliance with the Stevenson-Wydler Technology Innovation Act, the NIMH is instituting a formal system to (1) assess the final results from all supported research projects that have "a potential for useful application"; (2) ensure appropriate dissemination of such findings; and (3) provide technical assistance on the use of assessed findings to state and local governments and to the private sector. One purpose of the assessment phase, which includes initial reviews by in-house staff and a confirming review by nonfederal experts in the field, is to determine potential risks of dissemination and technical assistance activities. The director of the Office of State and Community Liaison, who is designated an NIMH officer for research and technology applications as required by the acts, carries primary responsibility for coordinating and reporting Stevenson-Wydler functions.

Evaluation of Public Health Effects of Assessments

Following Department of Health and Human Services (DHHS) guidelines, Human Subjects Committees composed of intramural and extramural scientists monitor patients undergoing treatment at St. Elizabeth's Hospital and the NIH Clinical Center. Patients who are given treatments that are suspected or known to cause adverse side effects are periodically surveyed on a national basis through the Applied Therapeutics Program of the Research Resources Branch, Division of Extramural Programs. Adverse effects of treatments are also monitored in clinics where the treatments are used and through physicians' communications to the Psychopharmacologic and Somatic Treatments Research Branch. The New Clinical Drug Evaluation Unit annual meeting focuses on findings of safety and efficacy of treatments from clinical trials.

To monitor public response, the Division of Communication and Education frequently includes a response card in NIMH publications, requesting feedback on the impact and effectiveness of the publications. The usefulness of the *Schizophrenia Bulletin* and the *Psychopharmacology Bulletin* is assessed by the number of subscriptions and by periodic surveys of subscribers.

Adverse Effects of Alcohol Use and Abuse: NIAAA

The list of health hazards known to be associated with alcohol consumption grows longer as more is learned about the ways in which alcohol, alone and in combination with other risk factors, affects the functions of the mind and body. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) conducts programs of research on the etiology, prevention diagnosis, and treatment of alcoholism and alcohol abuse, collects data concerning prevalence of alcohol use and abuse, and provides information to researchers, health care providers, and the public.

Mandate

The NIAAA is responsible for federal research programs dealing with the prevention and treatment of alcohol abuse and alcoholism. Established in 1971 by the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970, its legislative mandate is a part of the overall mandate of the ADAMHA. The institute is building a national alcohol research capacity for the purpose of developing a knowledge base that could lead to improved prevention and treatment efforts. The institute is also responsible for fostering the effective use of research information through dissemination of new knowledge to the health care community and others involved in prevention and treatment programs, as well as to the public. The NIAAA is required by Public

Law 98-24 to file a report to Congress every three years on the health consequences of using alcoholic beverages.

The NIAAA carries out a specific legislative mandate of the 1983 Alcohol and Drug Abuse Amendments to disseminate the results of alcohol-related research to various user communities through the Division of Prevention and Research Dissemination, and in part through the National Clearinghouse for Alcohol Information. The division is responsible for developing a broad data base containing information related to all aspects of alcohol abuse. It also provides information from the data base on request, produces a wide range of materials for use by researchers, health care providers, and the general public, and fosters outreach programs with public- and private-sector organizations in alcohol research and applications of research results.

Organizational Placement

NIAAA risk assessment activities take place in four divisions:

- The Division of Extramural Research supports basic and applied research activities through research grants awarded to medical schools, universities, independent laboratories, and other research organizations.
- The Division of Intramural Clinical and Biological Research conducts research on various aspects of the use of alcohol in its federal laboratories.
- The Division of Prevention and Research Dissemination is responsible for knowledge transfer and some assessment programs.
- The Division of Biometry and Epidemiology gathers data on the incidence, prevalence, and adverse consequences of alcohol use and abuse, and carries out its own program of research and analysis.

Agenda Setting

The institute continually reviews the research projects it supports in terms of scientific progress, areas of need, and subjects of interest to outside groups. The NIAAA also convenes special panels to evaluate the current status of institute-supported research and prevention activities and to make recommendations regarding needs and significant opportunities in each area.

To improve current understanding, clarify future needs in alcohol research, and determine what research results are ready for application, the NIAAA has begun to develop a new approach to agenda setting: the Alcohol Research Utilization System (ARUS). ARUS conferences are developed by a committee composed of scientists and experts in the alcohol field as well as an NIAAA program staff. Leading investigators known to be involved in a priority area of alcohol research are brought together for state-of-the-art conferences on the progress and implications of a body of research.

Risk Assessment Methods

The NIAAA conducts risk assessments through experimental, clinical, and epidemiological studies aimed at improving knowledge of the causes, effects, and nature of alcoholism and alcohol-related illness or injuries in order to develop more effective approaches to treatment and prevention. Research on inherited biochemical and physiological factors that affect individual susceptibility to alcoholism is an area of high priority. Studies of twins, half-siblings, and adoptees have produced definitive evidence that susceptibility to alcoholism is in part inherited by some individuals. Research with animal and human subjects is just beginning to isolate genetic markers of this susceptibility. Planned studies of children of alcoholics are of particular importance for identifying factors contributing to the higher risk of alcoholism in these individuals.

The NIAAA also conducts hazard characterization through research aimed at better understanding of the nature of alcohol-related problems. Tests measuring evoked electrical responses of the brain (EEG measurements) after exposure of the subject to various stimuli such as geometric patterns and human faces have demonstrated effects on the central nervous system that distinguish young adults with alcoholic parents as a group from others of the same age who have no family history of alcoholism. A set of intramural studies on pathological alterations of brain functioning associated with the alcohol withdrawal syndrome have indicated that changes in glucose metabolism occur in certain parts of the brain more than in other areas. These findings are consistent with clinical symptoms (e.g., nervous hyperexcitability) that occur during human withdrawal episodes and may indicate which regions of the brain would be most susceptible to pharmacological control of withdrawal symptoms in humans.

Exposure characterization at the NIAAA is conducted primarily by the Division of Biometry and Epidemiology, which develops and analyzes data on alcohol abuse and alcoholism in relation to patterns of occurrence, significance as factors in other medical disorders, significance as factors in injuries and death resulting from accidents and violence, and social and psychological consequences. A typical project was a study of patients in general hospitals to gather information on the incidence and prevalence of alcoholism and associated problems among patients hospitalized for other medical conditions. In addition to extensive collaboration with the National Center for Health Statistics (NCHS) the NIAAA has supported alcohol-specific data collection as part of the Public Health Service's (PHS) health statistics activity, including gathering alcohol-use data in its Health and Nutrition Examination Surveys (Chapter 8), with special attention to the aged and Hispanics. The NIAAA has also collaborated with the Department of Labor to estimate the prevalence of alcohol use and abuse in a national longitudinal survey of 11,000 young people and conducted two joint surveys with the NIDA on alcohol use among young people.

Risk determination at the NIAAA is based on the evaluation of research data. Such evaluation is made informally by individual researchers in their efforts to better understand the nature of alcohol use and abuse, and formally at ARUS conferences.

Scientific Review

Scientific review of alcohol-related research is conducted through several mechanisms. The ARUS and other research conferences provide one formal mechanism for review. Chartered initial review groups determine the scientific merit of each NIAAA-supported research project before a project is funded. Intramural research efforts are viewed by the board of scientific counselors, which is composed of leading research experts. In addition to internal review of all NIAAA research reports through consultation with researchers and institute staff, reports of alcohol health risk assessments in peer-reviewed scientific journals encourage eternal review.

Public Involvement

Public involvement in NIAAA health risk assessment activities is possible through lay representation on the NIAAA Advisory Council and through public participation at NIAAA conferences.

Description of Risk Assessment Reports

The NIAAA produces a variety of materials that report the progress and results of the institute's risk assessment activities. In general, these fall into two categories: those for scientists and health professionals and those for the general public.

Publications for scientists and health professionals—reports of NIAAA research findings, including conference and workshop proceedings, monographs, and technical reports—are intended to spread knowledge of alcohol research findings and to provide researchers and health professionals with up-to-date information so that they may provide better health care. The NIAAA also develops guides and manuals on the prevention of alcohol abuse.

Materials for the general public are primarily health education and promotion publications; some campaigns use the mass media. Although these materials provide accurate and comprehensive information about alcohol and its adverse effects, they generally do not contain extensive information on the underlying scientific evidence.

Mechanisms for Forwarding Results for Policy Decisions

The NIAAA is required to file a report every three years containing current information on the health consequences of using alcoholic beverages, with a brief description of current research findings made with respect to alcohol abuse and alcoholism. *The Fifth Special Report to the U.S. Congress on Alcohol and Health* was submitted to Congress during fiscal year 1984.

With the exception of the *Special Report to Congress*, no formal mechanisms are in place for forwarding risk assessment results to federal or state authorities with legal or regulatory authority over the sale and use of alcoholic beverages. Information from health risk assessment activities has been extensively utilized in developing policies and decisions about exposure to beverage alcohol. One of the best examples is the application to alcohol use when driving a motor vehicle, especially by young people. The effects of beverage alcohol on judgment and of motor reaction time, now well described and accepted, are widely used as a basis for legislation in both the state and federal sectors. Together with epidemiological data on the prevalence of auto accidents and deaths in the 18- to 21-year age group, this information is used to support legislation establishing a uniform minimum drinking age of 21.

Because of the well-known hazards of alcohol consumption, legislation was introduced in Congress to require alcoholic beverages to carry some type of health warning label. In 1980, the department was directed to prepare a report, including a recommendation on the issue of health warning labels on alcoholic beverages. A joint product of the DHHS and the Treasury Department, which has responsibility for alcoholic beverage tax revenue collection, the report to Congress did not recommend labeling alcoholic beverage containers at that time. The report included a thorough review of studies assessing health risks associated with consumption.

When a topic is judged to be of widespread public health significance, a surgeon general's advisory is prepared to inform the public and health professionals. One example is the "Surgeon General's Advisory on Alcohol and Pregnancy" (July 1981), recommending that women who are pregnant or considering pregnancy not drink alcoholic beverages and that these women take note of the alcoholic content of foods and drugs to minimize or eliminate their exposure to alcohol. This advisory has received wide attention, including distribution to most health professionals through the *Drug Bulletin* of the FDA.

Procedures for Disseminating Findings to the Public

The alcohol and health reports are widely disseminated to researchers, scientists, state alcoholism program directors, educational institutions, scholars, libraries, and practitioners in alcohol-specific and general health settings. The reports also form the basis for a variety of additional knowledge-transfer activities and materials, such as fact sheets, briefing materials, and educational modules.

The NIAAA project officer involved in producing informational materials also plans their distribution to researchers, practitioners, and the general public. Generally, these materials are widely distributed to the intended audiences, including state and local prevention agencies. In addition, the NIAAA's quarterly journal, *Alcohol and Health Research World* (with a paid subscription of more than 5,000), includes a wide range of alcohol-related information of interest to researchers, practitioners, and the public. The mass media are mainly used in campaigns aimed at specific public audiences.

Evaluation of the Public Health Effects of Assessments

The NIAAA frequently performs process evaluations on the dissemination procedures used by the institute in order to determine the effectiveness of information presentation and the availability, relative to need, of documents for public use. However, the

NIAAA does not have a formal mechanism for direct follow-up of the impact on public health of its risk assessments, due to the inherent difficulty of determining the impact of a specific NIAAA action on changes in public behavior.

Adverse Effects of Drug Use and Abuse: NIDA

The National Institute on Drug Abuse (NIDA) is the leading federal agency charged with creating activities to reduce the demand for illegal drugs and harmful health and social consequences of drug use. This general charge includes identifying and characterizing the adverse effects of drug use and abuse and communicating information on these effects to health care professionals and the public.

Mandate

The NIDA sponsors research on the etiology, prevention, diagnosis, and treatment of drug misuse and abuse. It gathers data on the extent of and national response to drug abuse problems and conducts basic investigations into the causes, effects and mechanisms of the action of illicit drugs. It also provides assistance to other federal agencies, states, and public and private organizations in their efforts to facilitate and expand programs for the prevention and treatment of these problems. In addition, the NIDA provides information to the public, to scientists, and to other professionals about research findings and drug abuse programs.

The Controlled Substances Act of 1970 requires that the DHHS conduct medical and scientific evaluations to assess the abuse potential of all legally manufactured drugs recommended by the attorney general for scheduling. Currently, the NIDA is the only agency within the PHS that carries out research on drug abuse potential.

Organizational Placement

Assessment of health risks associated with use and abuse of drugs occurs throughout NIDA's research divisions. The extramural research program includes the Division of Preclinical Research, the Division of Clinical Research, and the Division of Epidemiology and Statistics. Research in the Preclinical Division focuses primarily on research technology and the neuroscience and biomedical aspects of drug abuse, while activities of the Clinical Division include behavioral pharmacology studies, clinical investigations, and prevention research. The Division of Epidemiology and Statistical Analysis carries out research to estimate the prevalence and incidence of drug abuse and monitors trends in new drugs of abuse, abuse epidemics, and other drug abuse problems.

Based at the Addiction Research Center (ARC) in Baltimore, NIDA's intramural research program is responsible for the development of a basic science knowledge base, studies of abuse potential, and long-term clinical studies. The center has two research branches, the Preclinical Research Branch and the Clinical Pharmacology Research Branch. Research areas include chemistry, behavioral pharmacology, animal pharmacology, neuropharmacology, clinical pharmacology, epidemiology, and drug development/abuse potential.

Agenda Setting

The agenda for NIDA's extramural research program is determined by a series of priority-setting activities. Technology transfer provides feedback, and public interests and needs are monitored by NIDA's Division of Prevention and Communications. In designing strategies to promote research in recommended areas, the research divisions use all these sources of information.

The NIDA generally solicits research proposals in priority areas through grant announcements and RFAs announced in professional journals and in the *Federal Register*. Proposals are peer-reviewed by a committee of intramural and extramural scientists; funding allocation is based primarily on the merit scores of proposals.

The research agenda of the ARC is generally determined by the most prevalent drug abuse problems and most promising new developments requiring long-term follow-up. Often the NIDA will focus on drug abuse problems identified at interagency meetings, which may include the Drug Enforcement Administration, the FDA, the NIDA, and the State Department. The intramural research program is periodically reviewed by a board of scientific counselors.

Risk Assessment Methods

The NIDA risk assessment activities focus on three general areas: (1) monitoring of clinical reports of drug abuse (hazard identification); (2) basic science investigations of the abuse potential of psychotherapeutic and psychoactive drugs and determination of risks associated with abuse of illicit drugs (hazard characterization); and (3) determination of prevalence of drug abuse within the U.S.

population and identification of high-risk individuals (exposure characterization). Information from these analyses is used in overall risk determinations performed by agency scientists.

Drug Abuse Trends. In order to make available baseline information on drug abuse levels and patterns, the NIDA provides drug abuse data bases, including the Drug Abuse Warning Network (DAWN) project and the High School Survey. The monitoring of trends serves to identify new or increasing problem areas and to guide new research initiatives.

Characterization of Abuse Potential. NIDA's intramural research program, the ARC, has a primary responsibility for developing a basic science knowledge base in the abuse potential of drugs. Information from this knowledge base is used by outside agencies and investigators in the extramural research program, several of whom have research grants in this area.

Using dogs, rats, and monkeys, researchers determine the ability of a drug to maintain certain kinds of self-administration behavior and then characterize addictive properties of drugs by means of animal and in vitro tests. New drugs with unknown abuse potential are administered to animals already trained to respond in a specific way to a specific drug (e.g., cocaine) and responses are noted, since drugs with action similar to the training drug elicit a similar response from the animals. Those that do not have a similar action may then be tested in other animal systems for a different type of effect.

Behavioral tests to determine the strength of reinforcing properties of drugs address the environment and activities associated with use of a drug. The environments of animals are altered, and drugs are then administered under different circumstances. In some cases (e.g., with smoking and nicotine), significant changes in self-administration behavior are noted. Such types of animal studies may be performed in parallel with human studies.

Determination of Risks Associated with Drug Abuse. Basic drug research helps to determine how drugs produce their effects in the body, particularly in the brain and central nervous system (CNS). Research involves sites of action, underlying biological mechanisms, metabolism of drugs, dose-response relations between drugs and pain, sleep, cognition, mood, behavior and performance, and drug toxicity. In addition to science studies, which include in vitro studies of drug mechanisms and toxicity, use of animal models to determine dose-response relationships and toxicity, and human studies of behavior and performance, studies of clinical reports of drug abuse provide information on adverse physiological and psychological consequences.

Drug Abuse Prevalence and High Risk Identification. NIDA's three drug abuse data bases, the Drug Abuse Warning Network, the National Household Survey, and the High School Survey, determine drug abuse levels. Etiologic research assesses variables that may predispose some individuals to above-average risk of drug abuse.

Risk Determination. In general, overall risk determinations are carried out through internal reviews and state-of-the-art conferences that bring together intramural investigators and outside experts for a formal review of all research in a specific area and produce extensive reviews published in the research monographs series. Research results are evaluated not only with regard to what is known, but also with attention to implications for public health and further research needs.

Scientific Review

Branch chiefs and project officers review research results in the intramural and extramural research programs. Project officer reviews of their research areas are presented to peers periodically, while research in the intramural program usually leads to articles for peer-reviewed journals.

Both the intramural and extramural research programs participate in the Research Analysis and Utilization System (RAUS), which retains experts in specific research areas to review and evaluate all research on a particular topic. Extensive reports from RAUS conferences are presented in the RAUS monograph series. A group of renowned scientists comprise the NIDA editorial advisors, who provide peer review and advice on NIDA publications.

Public Involvement

Members of the public occupy several positions on the NIDA Advisory Council and play an important role in NIDA priority setting. NIDA representatives periodically meet with members of the public and private sector to monitor public needs for new research and new media and information campaigns. All NIDA research conferences are open to the public.

Description of Risk Assessment Reports

In addition to presenting their research at professional meetings, investigators are encouraged to publish their research results in peer-reviewed journals. The NIDA produces several types of reports based on research results of institute-sponsored programs. Following periodic review, extramural project officers report in writing on results from the grants that they monitor. The NIDA conducts fifteen to twenty technical reviews on research issues annually. The *Research Monographs* series, prepared by the research divisions and published by the institute's Office of Science, provides critical reviews of research subject areas and techniques. The NIDA also operates the Research Analysis and Utilization System (RAUS), described above. The results of RAUS conferences published in the RAUS monographs series typically develop a summary of the body of knowledge in a research area, address current data gaps, and recommend future research.

The NIDA also produces a variety of publications for more general use, including educational manuals for health care professionals and general information and hazard warnings for the lay public.

Mechanisms for Forwarding Results for Policy Decisions

Three types of policy decisions may be affected by NIDA's activities in health risk assessment: regulatory/law enforcement policy, research policy, and information transfer policy. In the first place, the NIDA provides information on the abuse potential of substances to the FDA for use in regulating potentially addictive substances before they are released to the public. The information is often relevant to concerns of the Department of Justice, which may use it in placing restrictions on the distribution of potentially harmful drugs.

Research planning depends largely on the results of NIDA assessments of the stage of current research findings and inquiries to the field and public. An important function of the RAUS and technical reviews and project officer reviews is to state clearly the data gaps and areas of research needs so that these needs may be incorporated into NIDA's priority-setting process. Finally, NIDA assessments are used jointly by the Office of Science, the Office of Communications, and the director's office in making decisions or in formulating recommendations for PHS policy decisions.

Procedures for Disseminating Findings to the Public

Dissemination procedures used for the various reports described above vary with the target audience. Brochures and pamphlets prepared for the general public are disseminated by mass mailings to state agencies, prevention organizations, schools, businesses, industries, national professional organizations, and others. On the other hand, NIDA reports written for educated lay and professional audiences, such as the *Research Monographs* series, are disseminated by means of a mailing list of researchers, educators, administrators, and libraries, announcements in newsletters to state and local drug abuse agencies, and listings in a catalog of publications.

Evaluation of Public Health Effects of Assessments

The institute attempts to evaluate the public health consequences of public education campaigns by monitoring behavioral and additional changes toward drug abuse in the general population. Through attitudinal surveys and monitoring of the DAWN system, the institute obtains information on trends and emerging problems in drug misuse and abuse. The NIDA does not, however, have a formal mechanism for tracking the impact of its research/risk assessment programs on government regulatory policy.

CASE STUDIES

Genetic Factors and Schizophrenia: NIMH

Schizophrenia has long been known to occur frequently in close relatives of patients, and many studies of inheritance patterns have confirmed a genetic basis for this disease. Not all individuals having a genetic risk for developing schizophrenia are struck by the disease, however, and individuals with no apparent family history may suffer chronic schizophrenic episodes as well. Specific gene mechanisms and their importance relative to environmental influences are as yet unclear.

The NIMH has sought to increase public awareness of schizophrenia and foster further research into both its causes and its treatment. In 1981, the NIMH issued a summary report on genetic factors and schizophrenia, developed from the analytic elements discussed below.

Hazard Identification

Approximately 0.85 percent of the general population of the United States and Western Europe suffer a schizophrenic episode at some time. However, the incidence of schizophrenia within family groups is far in excess of this base rate, and a variety of studies have positively identified schizophrenia as in part a genetically based disorder. Studies in this area are of three general types: family studies, twin studies, and adoption studies. The first two are components of the hazard identification phase of a risk assessment; the latter is included in hazard characterization.

Family Studies. Family studies are based on the principle that biological relatives have a greater number of genes in common than do unrelated persons, so that diseases with no genetic basis will appear more frequently in affected family groups than in the general population. Several family studies have shown this to be the case for schizophrenia:

- Among close relatives of a schizophrenic, the risk of developing schizophrenia ranges from two to forty-six times the risk in the general population.
- First-degree relatives (parents, siblings, children) of a schizophrenic individual have a greater risk of developing schizophrenia than second-degree relatives, who have a risk greater still than third-degree relatives.
- Offspring of two schizophrenic individuals have a greater risk of developing schizophrenia than offspring of one schizophrenic and one unaffected individual.

Twin Studies. There are two types of twins: monozygotic or identical twins, derived from a single fertilized egg; and dizygotic or fraternal twins, derived from two fertilized aggs. Monozygotic twins have virtually identical genetic makeups, whereas dizygotic twins are no more similar genetically than singleton siblings. Thus, genetically based diseases are more likely to appear in both identical twins than in both fraternal twins. In nearly a dozen such studies concordant schizophrenia has been observed in up to 58 percent of identical twins, while concordance in fraternal twins has been reported to be no higher than 26 percent. These findings confirm the expected association, but the lack of concordance in almost half of the identical twins suggests that the development of schizophrenia has a large environmental basis as well as a genetic basis.

Hazard Characterization

Adoption Studies. Because siblings in the same family are likely to be exposed to similar environmental circumstances, a major methodological flaw in both the family and twin studies is their inability to separate fully the environmental and genetic influences in the development of schizophrenia. Adoption studies, which examine the incidence of schizophrenia in children of schizophrenic parents who have been removed from their homes and placed in different environments, circumvent this difficulty. They demonstrate that children of schizophrenics who have been adopted by nonschizophrenic parents have the same risk of developing schizophrenia as children who remain with their biological parents. Thus, these studies strongly support the presence of a genetic factor in the development of schizophrenia.

- Children of schizophrenic parents placed in foundling homes were compared with matched control children placed in the same foundling homes. Of 47 adopted children of schizophrenics, five eventually developed a schizophrenic disorder; none of the control children were affected.
- In Denmark, 30 percent of adoptees of schizophrenic biological parents developed schizophrenic disorders, as opposed to 17.8 percent of a control population.
- Biological relatives of schizophrenics have a greater incidence of schizophrenia than their adopted relatives. If environmental influences were the primary factors involved in the development of schizophrenic disorders, similar incidences of affected individuals among adopted and biological relatives would be expected.

Several other adoption studies have demonstrated that genetic factors are more important in the development of schizophrenia than environmental factors.

- A study of 63 paternal half-siblings of schizophrenic individuals and 64 matched controls found that 14 paternal half-siblings of schizophrenic individuals developed a schizophrenic disorder, whereas only 2 individuals in the control group were affected. As these half-siblings are related through the father, this study rejects the hypothesis of a solely maternal (prenatal or perinatal) effect in the etiology of schizophrenic disorders.
- A comparison of one group of schizophrenic children raised by adoptive parents and another group raised by biological parents revealed a greater incidence of schizophrenia in the biological parent group. Since a number of the children raised by adoptive parents did develop schizophrenia, however, it also revealed that parental psychopathology is not a necessary precondition for the development of schizophrenia disorders.
- A group of adoptees with no family history of schizophrenia

who were raised by schizophrenic adoptive parents were found to have no greater incidence of psychopathology than the control group. This study suggests that children with no family history of schizophrenia who are raised in the home of a schizophrenic do not show an elevated risk of developing schizophrenic disorders.

Studies of Mechanisms of Inheritance. It is clear that schizophrenia, like many other heritable traits, is not transmitted according to simple Mendelian genetics. Several researchers have used quantitative genetic approaches to investigate the mode of inheritance of the gene or genes involved in the development of schizophrenia.

- One model developed to account for some of the characteristics of schizophrenia—all-or-none expression of the disease and a non-Mendelian mode of inheritance—presupposes that underlying the disorder is a continuously distributed "liability" that encompasses all endogenous and exogenous factors predisposing to the disorder. The distribution of liability is represented by a bell-shaped curve. The model also includes a threshold concept, with the point that separates those who are affected from those who are not being located near one end of the curve.
- Family and twin data appear to be compatible with a single gene model that incorporates a threshold concept.
- Two additional genetic models have been developed, one using a single major locus model and one using a polygenic model. Neither of the models agrees accurately with the observed data. However, both models suggest that a limited proportion of the affected population is homozygous for the disorder; i.e., a large proportion of schizophrenics are either heterozygous for the disease, or the occurrence of the disease is influenced by environmental factors.

Exposure Characterization

Exposure characterization for a genetic cause of disease consists first of estimates of the frequency of inheriting the gene(s) that predisposes an individual to the disorder, perhaps supplemented by data on gene-environment interaction. Estimates of gene frequencies have been generated using the models described in the preceding section:

- Given the prevalence rates among different classes of relatives of affected individuals, the bell-shaped model for "liability" was used to estimate that the heritability of the liability is 85 percent.

- Using a single gene model with a threshold, the gene promoting schizophrenia was calculated to have a frequency of approximately 10 percent, and a threshold such that at least 50 percent of homozygotes would be affected.

Risk Determination

Based on a review of the information presented in the preceding sections, NIMH scientists reached the following conclusions:

- Genetic factors are involved in the etiology of schizophrenia.
- Genetic predisposition is not a sufficient condition to produce the disorder; both genes and environment are important etiologic factors.

In reaching these conclusions, researchers considered the scientific uncertainties associated with the studies. The adoption studies, for example, suffer from various sampling and other methodological problems associated with a dependence on medical records for gathering information. Nevertheless, these studies of discrete populations in different areas of the world strongly suggest that a genetic factor is important in the etiology of schizophrenia. Hence quantitative genetic models do have limited uses in understanding the biochemical and neurophysiological mechanisms of inheritance of the schizophrenic trait.

Lithium: NIMH

Lithium is used in the treatment of patients with mood disorders that are bipolar (characterized by episodes of mania and depression) or unipolar (characterized by depression only). Regarded as a highly effective treatment for acute mania, lithium is the drug of choice for preventing or attenuating recurrences of bipolar disorders. It may also be effective in reducing the frequency and intensity of depressive recurrences in unipolar mood disorders, although the evidence is not as conclusive as with bipolar disorders. In general, lithium is not the treatment of choice for ongoing depression, though it may be effective in cases that do not respond to other treatments.

The NIMH has studied the safety and efficacy of lithium through a combination of laboratory research and two multihospital studies (one in collaboration with the Veterans' Administration (VA)). The

NIMH also recently sponsored a consensus development conference on *Mood Disorders: Pharmacologic Prevention of Recurrences,* which provided a consensus statement on the safety and effectiveness of lithium.

Hazard Identification

The primary side effects of both acute and long-term exposure to lithium are similar: thirst, polyuria, tremor, diarrhea, and weight gain. Although memory problems, tiredness, and a dulling of senses have been reported, these have not been entirely separated from symptoms of the disorder. Long-term lithium therapy has produced minor renal tubular defects and impaired thyroid function (hypothyroidism).

In 1968, the NIMH and the VA jointly initiated an eighteen-hospital collaborative project on lithium carbonate therapy of affective disorders. The first clinical phase of the VA-NIMH project compared the effectiveness of lithium carbonate to that of chlorpromazine hydrochloride in patients with acute mania or schizo-affective disorder, manic type, finding that:

- Mild side effects appeared in most patients taking lithium, but few of these reactions were serious enough to warrant even a temporary reduction in dosage.
- Toxic confusion appeared in 6 percent of lithium-treated highly active or excited schizo-affective patients, but the symptoms (disorientation, confusion, reduced comprehension, lack of continuity of thought) were usually preceded by a steadily progressive or sharp rise in lithium dosage and remitted within a few days following reduction or withdrawal of the treatment. No toxicity was reported in mildly active lithium-treated schizo-affective patients.
- The most common side effects of lithium were gastrointestinal symptoms (nausea and diarrhea), tremor or hyperactive deep tendon reflexes, dry mouth, and dizziness.

The second phase of the VA-NIMH project, a two-year, placebo-controlled trial evaluating the prophylactic efficacy of lithium in the manic patients who had participated in the initial (acute) phase, found that:

- Side reactions appeared in more than 60 percent of patients treated with lithium carbonate. The most common reactions were diarrhea, fine hand tremor, nausea, muscle weakness, hyperactive deep tendon reflexes, anorexia, and somnolence.

In most cases these symptoms caused little difficulty and disappeared without adjustment in dosage.

- Twenty-four percent of the manic-depressive (bipolar) patients had reactions severe enough to require dosage reduction or withdrawal. Only one of the 18 patients suffered side effects severe enough to require permanent discontinuation of lithium carbonate.
- Eighteen percent of the depressive (unipolar) patients receiving lithium had reactions severe enough to require dosage reduction or temporary drug withdrawal.

In 1982 NIMH completed a five-center collaborative clinical study of long-term maintenance drug therapy in recurrent affective illness, which evaluated the prophylactic efficacy of lithium carbonate, imipramine, or lithium plus imipramine in bipolar patients and of lithium, imipramine, lithium plus imipramine, or placebo in unipolar patients. Treatments assigned on a randomized double-blind basis continued for a mimimum of two years after recovery from an acute episode.

- Approximately 16 percent of the bipolar subjects and 14 percent of the unipolar subjects receiving lithium experienced side effects of more than mild severity during prophylactic treatment, including dry mouth, fine tremor, constipation, polyuria and/or polydipsia, lethargy, headache, and excessive sweating.

Hazard Characterization

Several clinical studies have shown that slight to moderate reduction of renal concentrating ability occurs in up to 50 percent of patients and that long-term lithium treatment may lead to significant reduction in renal efficiency. In these patients, symptoms of thirst, polyuria, and nocturia often develop; up to 50 percent of patients may develop a syndrome of nephrogenic diabetes insipidus.

- A study of biopsies for renal morphology of approximately 150 patients showed nonspecific, irreversible lesions in the tubules and interstitial tissues of kidneys in 15 percent of patients given lithium for more than five years, but similar lesions have been found in kidneys of patients before they received lithium treatment. The clinical significance of these morphological changes is not known.
- Fifteen other studies (five of which included controls) of over 1,000 patients showed no marked progressive impairment of

renal glomerular function even after 10 to 15 years of lithium treatment.

The importance of the type of lithium preparation and the daily dosage schedule (e.g., taken all at once before bedtime or spread out over the course of the day) is unclear. Data concerning the duration of prophylactic treatment are also lacking and should be determined on an individual basis.

Exposure Characterization

An important aspect of exposure characterization is the identification of persons who may be at increased risk of adverse effects following exposure. Lithium may present special risks in pregnant and nursing women. Risks for lithium prophylaxis have not yet been determined in children and adolescents, but several preliminary studies suggest that problems are similar to those seen in adults.

Risk Determination

The consensus development conference panel concluded, primarily from the two NIMH collaborative studies, that the beneficial effects of lithium treatment for affective mood disorders far outweigh the adverse side effects. At the same time, it recommended that special care be taken when administering lithium to elderly patients, pregnant or nursing women, patients with reduced renal concentrating ability, and others in whom the fluid-electrolyte balance must be monitored. According to the panel, the side effects of long-term use (over 6 months) can be controlled by lowering doses or treating side effects with supplementary medication, although some patients may require discontinuation of medication.

The consensus panel found that the long-term use of lithium for prevention of recurrence does not pose risks significantly different from those of short-term use except for impaired thyroid function, which may increase in frequency over time on prevention therapy, where large doses are administered over shorter periods. The side effects are usually fully or partly reversible when the treatment is discontinued, and most patients respond favorably to various specific treatments for side effects during continued lithium treatment. Higher doses and longer duration of treatment may lead to increased risks of renal and neuromuscular effects and of lithium poisoning.

Fetal Alcohol Syndrome: NIAAA

Fetal alcohol syndrome (FAS) is a characteristic pattern of congenital abnormalities including some with prenatal onset and some postnatal developmental and performance deficiencies. The syndrome consists of behavioral, craniofacial, limb, and neurological anomalies and, in nearly 50 percent of reported cases, cardiac septal defects, genital abnormalities, and hemangiomas.

In September 1977, the NIAA published a public health advisory on the hazards of maternal alcohol consumption during pregnancy in the FDA Drug Bulletin, following a state-of-the-art conference on the effects of alcohol on fetal development that was convened by the institute. A second public health advisory on FAS was issued in July 1981 by the surgeon general. The following discussion focuses on the analysis conducted in support of the recommendations.

Hazard Identification

Studies that provide evidence that FAS occurs as a clinically observable entity in human beings include:

- A retrospective study of forty-one patients demonstrating FAS, all of whom were born to chronic and severely alcoholic women who drank throughout their pregnancy.
- A study of the intellectual development and motor performance of twelve offspring of chronic alcoholic women, which found that all but one of the children had impaired intelligence.
- A study of 127 offspring from sixty-nine French families suffering from chronic alcoholism. Adverse health effects were reported only in cases of maternal alcoholism, and included malformations in twenty-five children. The facial profile of the children was characteristic of FAS, many were hyperactive, and an average IQ of ±70 was reported.
- Two postmortem studies of children with FAS symptoms revealed extensive developmental anomalies in the heart and brain.

The frequency of individual case reports of FAS was cited as additional evidence for the occurrence of this syndrome.

Epidemiologic studies in the United States have suggested that alcohol consumption is associated with a wider spectrum of adverse fetal outcomes than just FAS. In a cohort study, 7.8 percent of alcoholic nonsmokers were found to have delivered small-forgestational-age infants. Another study found that infants born to heavy women who drank heavily demonstrated four times the frequencies of major congenital anomalies and twice the frequency of minor anomalies as offspring of either moderately drinking or rarely drinking women.

Several animal studies also provided information on the effects of alcohol on pregnancy.

- Three studies reported dose-related effects of alcohol on prenatal mortality and on frequency of malformations in mice. Many of the defects were similar to those reported in FAS patients.
- Similar findings were also reported in dogs.

The animal models revealed a range of adverse effects closely resembling FAS in humans and significantly elevated teratogenesis in alcohol-fed animals.

Hazard Characterization

An important aspect of the effects of alcohol on fetal development is the relation between dose and response—that is, the relation between the amount and frequency of alcohol consumption and the likelihood and severity of FAS in the fetus. However, the retrospective analyses used to identify FAS have limited ability to characterize the dosage and types of alcohol consumption in which FAS and FAS-related effects become a significant risk. Most of the information on the relation between dose and response has come instead from animal models and prospective epidemiologic studies.

Prospective studies providing information on the relation between dose and response citied in the report are as follows:

- A prospective study of 9,236 pregnancies between 1963 and 1969 revealed a significant increase in stillbirths among women categorized as heavy drinkers (consuming 1.5 ounces or more of absolute alcohol daily). Infants born to the heavier drinkers were reported to have lower birth weights and smaller placentas, though no significant variation in frequency of congenital malformations was observed.
- A prospective study of 263 members of a Health Maintenance Organization (HMO) showed a significantly smaller birth weight for children of women who reported consuming an average of one ounce or more of absolute alcohol per day during their prepregnancy period.

- A hospital-based study included information on amount of alcohol consumed as well as use of drugs, smoking and nutritional status, and demographic data. Women were categorized as heavy (9 percent), moderate (39 percent), or rare (52 percent) drinkers. The heavy drinkers reported consuming an average of 5.8 ounces of absolute alcohol per day. Heavy drinkers had social characteristics similar to the rest of the sample population except for age (they were significantly older) and smoking habits (60 percent of heavy drinkers reported smoking one or more packs of cigarettes per day). Offspring of the heavy drinkers had significantly shorter lengths, less weight, and smaller head circumferences, as well as significantly more frequent congenital malformations.
- A study at the University of Washington included information on the quantity and frequency of alcohol consumed, diet, smoking, and drugs and other medication taken prior to and during pregnancy. Women whose reported average consumption of absolute alcohol exceeded one ounce per day were identified as possibly at high risk for adverse pregnancy outcomes. Different subsamples of the women and their offspring were studied at various times during the study. In one subsample consisting of 74 women from the high-risk group, and 90 mothers with a lower level of alcohol intake, eleven infants were judged to show some clinical features of FAS. Nine of these were born to women in the high-risk group, and two of the nine had the full pattern of FAS abnormalities.
- Two studies have reported that spontaneous abortion is associated with alcohol consumption. The first found an association when 1 ounce of absolute alcohol was consumed twice per week, while the second reported an association of abortion with consumption of 0.5 to 1 ounce absolute alcohol per day.

Exposure Characterization

Estimates of per capita alcohol consumption in the United States based on sales and excise tax data, surveys of self-reported consumption among adults and among youth and young adults, and surveys of alcohol consumption during pregnancy yield the following results:

- Estimates based on sales suggest an annual per capita consumption level of 2.77 gallons per year or approximately 1 ounce of absolute alcohol per day. These estimates must be interpreted cautiously however, because of large person-to-person differences in drinking habits, and effects on the estimates of differences across states in drinking ages and out-of-state purchasers.

- One-third of American adults describe themselves as abstainers (consumed not a single drink in the year prior to the survey); another third describe themselves as light drinkers (consumed on average not more than .21 ounces of absolute alcohol per day; and the remaining third were either moderate drinkers (.21-.99 ounces of absolute alcohol per day), or heavy drinkers (consumed more than 1 ounce of absolute alcohol per day, or the equivalent of two drinks per day). Men drink more than women, and younger adults generally drink more than older adults.
- Surveys of youth and young adults have shown that more than 90 percent of high school seniors have consumed alcohol at least once. Six percent reported daily or nearly daily use during the month prior to the survey, and 41 percent reported drinking five or more drinks on one occasion during the two-week period preceding the survey.
- Recent surveys have studied alcohol consumption in a sample of married women who gave birth to live infants in 1980 and a sample of women whose pregnancies terminated in fetal death. Preliminary analysis of 4,405 mothers giving live births show that women substantially reduce their alcohol consumption during pregnancy. Forty-one percent of the women surveyed reported abstention from alcohol prior to pregnancy, a number that increased significantly to 61 percent during pregnancy. Levels of moderate/heavy drinking decreased from 12 percent of women prior to pregnancy to approximately 2 percent during pregnancy.
- In Goteborg, Sweden, an incidence of one out of 600 births for confirmed FAS and an equal number of probable FAS cases was reported for the 7,600 births in that city over a 17-month period. Data from Roubaix, France, from 1975 and 1976 indicated a similar incidence rate based on 6,927 total births.

Risk Determination

The convincing evidence that alcohol is a risk factor for fetal outcome provided by a large number of case reports of FAS and the studies of alcohol exposure during pregnancy in animals and humans led to the publication of the two public health advisories mentioned above. At the request of Congress (Public Law 96-180), a report titled "Report to the President and the Congress on Health Hazards Associated with Alcohol and Methods to Inform the General Public of the Hazards" was prepared jointly by the

Department of the Treasury and the DHHS. The report reviewed knowledge on alcohol and pregnancy that was current both before and after the 1977 health advisory. The joint report from the two departments recommended that the surgeon general issue the updated advisory on alcohol use in pregnancy that appeared in June 1981. Department scientists, however, reached no conclusion about the existence of a threshold for the effects associated with alcohol consumption. This absence of a clear indication of a threshold is reflected in the vague recommendation of the surgeon general's advisory: "The Surgeon General advises women who are pregnant (or considering pregnancy) not to drink alcoholic beverages and to be aware of the alcoholic content of foods and drugs."

PCP-Induced Psychosis: NIDA

Phencyclidine (PCP), or angel dust, was originally developed for use as a human anesthetic in the 1940s by Parke, Davis & Co. While human use was never approved, the drug is currently produced and used legally as a tranquilizing agent in veterinary medicine. PCP has also become one of the primary drugs of abuse in many American cities.

In 1978 the NIDA sponsored a state-of-the-art conference on PCP abuse that included an analysis of the adverse health effects, effective treatment methods, and current levels of PCP abuse.

Hazard Identification

One adverse health effect of the drug is a schizophreniform psychosis that follows PCP exposure in some individuals and generally persists for more than a day. The psychosis is generally most severe at the onset, but may continue for days or weeks without further PCP exposure.

Evidence that use of PCP could result in psychosis in humans was derived primarily from three studies.

- In the fall of 1973, admissions for an unusually long and treatment-resistant form of a schizophrenic psychosis tripled at a community health center in Washington, D.C. In the following months, admissions of individuals with this psychosis continued to increase, until they constituted one-third of all admissions by February 1974. All of these patients were later found to have smoked PCP-laden cigarettes prior to the onset of pyschoses.

- A study of residents in a therapeutic community for the treatment of polydrug abusers reported that 76 percent of chronic PCP users had suffered bad experiences with PCP. These experiences included numbness, loss of motor control, paralysis, confusion, sensory distortions and loss of consciousness, cramps and nausea, auditory hallucinations, violent behavior, paranoia, and loss of judgment and memory.
- Examination of the clinical course of the treated psychosis led to the delineation of three distinguishable phases: an initial phase, characterized by a period of violent, psychotic behavior, generally lasting for about five days; a second phase, in which the patients remained restless and unpredictable but displayed a greater level of self-control; and a final phase characterized by rapid personality reintegration and disappearance of thought disorders and paranoia.

Hazard Characterization

Early clinical testing provided the initial characterization of the psychosis:

- PCP produces brief psychotic episodes nearly indistinguishable from schizophrenia in individuals with no previous psychiatric record.
- The psychosis ensues shortly after exposure to PCP.
- The psychotic condition is manifested in such effects as altered body image, thought disorders, estrangement, autism, and occasional catatonia.

Additional studies of the mechanism of PCP-induced psychosis and the importance of dose were summarized in the NIDA review of PCP research. Since the pharmacology of PCP has not been completely characterized, however, the mechanism of PCP psychosis is also unknown. Investigators have reported that PCP is likely to act by producing an organic brain disorder, and thus may be associated with distinct personality changes.

PCP-associated psychosis is merely one in a range of PCP reactions frequently reported in treatment centers. Other adverse reactions also appear to be dose-dependent, with both the number and severity of adverse effects increasing with dose.

Exposure Characterization

Differences in potency, purity, and exposure routes of PCP make a precise quantification of "typical" dose levels impossible. The PCP

"Appraisal" report includes several papers summarizing epidemiologic or broad survey studies of individuals using PCP. The following conclusions were made as a result of these studies.

- PCP use is growing nationally.
- Those most at risk of PCP use are young, Caucasian males.
- Use of PCP is a diverse phenomenon with wide variations in both the amount taken and frequency of use.
- One study noted that out of a sample of twenty-five chronic PCP users, only one had experienced the psychotic PCP reaction, and speculated that, given the wide availability and popularity of PCP, the psychosis was in all likelihood a relatively rare occurrence. It was unclear at that time whether some specific risk factors for the PCP psychosis led to a greater susceptibility in some users.

Risk Determination

Based on a review of the data summarized in the preceding sections, NIDA scientists reached the general, qualitative conclusion that a temporary mental disturbance (PCP psychosis) may last for days or weeks. No other overall conclusions have yet been reached about the likelihood of such an occurrence or the factors that may place an individual at higher risk of developing this effect.

Marijuana: NIDA

Marijuana is the most popular illegal psychoactive drug commonly abused in the United States; in 1979, over 50 million Americans had used marijuana at least once in their lives. Marijuana is a major health problem because acute intoxication with marijuana impairs normal mental functioning and poses the risk of adverse effects on most of the major organ systems of the body. Until 1983, the NIDA produced annual reports for Congress summarizing information on the health effects of marijuana. These reports, which also provide a basis for NIDA information outreach campaigns and serve as a health advisory against the use of marijuana, were developed from data and NIDA staff analysis discussed below.

Hazard Identification

Respiratory Effects. Inhaled marijuana smoke can impair respiratory tract and lung macrophage function, although effects appear to be reversible. Low doses (one marijuana cigarette) generally stimulate bronchodilation and ventilation in conjunction with an increase in metabolic rate and a heightened response to carbon dioxide as a regulatory stimulant. Larger doses generally result in airway obstruction and may depress ventilation and response to carbon dioxide stimulus. Heavy chronic exposure has resulted in chronic inflammatory changes in the bronchi and uvula, frequently in association with chronic sinusitis.

Acute exposure of alveolar machrophages to marijuana smoke in vitro appears to cause a reduction in phagocytic activity. Evidence cited to support a cause-effect relation between marijuana and these effects includes:

- Significant changes have occurred in explants of lung tissue exposed to marijuana smoke in culture.
- Studies have revealed a depressed bactericidal activity in rat lung tissues exposed to marijuana smoke.
- Chronic bronchitis is frequently reported by some subjects, though it is difficult to separate the effects of cigarette smoke from those of marijuana.

Several studies have suggested that marijuana may pose a carcinogenic risk in long-time users, though the evidence for carcinogenic potential is far from conclusive. The supporting experimental evidence, which comes primarily from in vitro tests, may be summarized as follows:

- The chemical composition of smoke from tobacco and marijuana have qualitative similarities.
- Human lung cells exposed in culture to fresh marijuana smoke for two months showed stimulation of DNA synthesis, increased mitotic indices, and proliferation of cells with four times the DNA content of control cells or those exposed to tobacco smoke.
- U.S. servicemen who smoked 50 grams or more of hashish per month showed evidence of preneoplastic changes including a reduction in cilia, increased basal epithelial cells, and atypical cells.

Cardiovascular Effects. No permanent adverse cardiovascular effects have been demonstrated following chronic exposure to marijuana. However, marijuana has been found to increase the work of the cardiovascular system in some individuals, an increase that may pose a significant risk to individuals with heart disorders.

- Delta-9-THC (the main psychoactive component) has been reported to effect a prompt increase in heart rate (up to 90 beats per minute), lasting up to one hour.

- Acute exposure to delta-9-THC has been found to increase blood pressure in some individuals lying supine. Chronic administration can cause decreased blood pressure.
- Acute administration of delta-9-THC has caused changes in the ECG of subjects.
- The hypertension caused by exposure to delta-9-THC has been associated with an increase in systemic vascular resistance.

Reproductive Effects. A 1982 technical review collected these findings on the effects of marjuana on the reproductive system.

- A 1974 study of 29 chronic marijuana users revealed significantly decreased sperm counts and testosterone levels when compared with controls, suggesting a dose-dependent suppressive effect.
- Sperm counts were significantly lowered in 16 subjects following chronic administration of marijuana. Decreased sperm motility and increased abnormal sperm were reported prior to the decrease in sperm count.
- Plasma LH and FSH were significantly lowered following acute administration of delta-9-THC in rhesus monkeys.
- Marijuana administered to rats significantly lowered sperm counts.
- Marijuana and its derivatives are antagonistic to male hormones, though the specific mechanisms are not clear.
- Suppressed ovarian function, estrogen activity, and levels of RNA and sialic acid have been reported following administration of marijuana extract to rats and mice.
- Appropriately timed administration of delta-9-THC to rats may block ovulation.
- Suppression of plasma levels of FSH and prolactin have been reported following preovulatory administration of delta-9-THC in rats.
- Delta-9-THC administration in ovariectomized rats and rhesus monkeys has been reported to result in depressed LH plasma concentrations.
- Precoital administration of delta-9-THC has been reported to block postcoital LH surge and ovulation in the rabbit.
- Delta-9-THC administered to rhesus monkeys during the follicular phase produced long periods of amenorrhea, absence of midcycle LH surge, and anovulatory progesterone levels.

Birth Defects and Teratogenicity. Delta-9-THC readily crosses the placenta, and preliminary reports suggest a potential for teratogenicity:

- Subcutaneous injection of crude marijuana extract in pregnant hamsters and rabbits caused development effects in embryos, including malformations in the brain, spinal cord, forelimb, and liver.
- High maternal doses of delta-9-THC produced significant fetal growth retardation in mice; 12.1 percent of the live fetuses were malformed.
- A high rate of offspring loss during pregnancy or in the early postnatal period was reported in female monkeys given an oral dose of delta-9-THC for one to four years.

Hazard Characterization

Respiratory Effects. Chronic exposure to marijuana is associated with several effects, including chronic bronchitis, increased airflow resistance, and decreased pulmonary function.

- A study of 31 American soldiers who smoked large amounts of hashish for a period of 6 to 15 months revealed several chronic respiratory ailments including bronchitis, sinusitis, asthma, and rhinopharyngitis. A decrease in exposure to hashish alleviated the symptoms.
- A study of 74 persons who smoked marijuana for two to five years, frequently several times per day, revealed a significant increase in resistance to airflow in the large airways.
- A study of 200 American soldiers in West Germany who sought medical attention following chronic heavy smoking of hashish revealed pharyngitis, sinusitis, bronchitis, and asthma. Subjects with pharyngitis usually smoked less than 25 grams of hashish monthly; subjects with bronchitis and asthma generally consumed more than 50 grams per month.
- Twenty high-dose hashish smokers were reported to have chronic bronchitis accompanied by abnormal pulmonary function, exhibited by a vital capacity of 15-40 percent below normal for age and sex. Biopsy of bronchial mucosa in six subjects revealed abnormalities similar to those of older heavy cigarette smokers. The biopsies also showed atypical cell types not found in tobacco smokers.

Lung Cancer. Several studies have characterized a potential risk of lung cancer from marijuana smoke, though no increase in the incidence of lung cancer in chronic marijuana users has been reported. A latency period may be involved such that increased incidence has not yet occurred.

- Marijuana smoke has been reported to contain 90 percent more carcinogenic hydrocarbons than tobacco smoke.
- Dose-related mutations have been produced in four out of five test strains of bacteria exposed to extracts of marijuana smoke particulates.

Exposure Characterization

Exposure levels have been determined largely through two continuing nationwide monitoring studies sponsored by NIDA, one based on general household population samples and the second on populations of high school seniors. The National Household Surveys, conducted annually or biannually with samples varying from 3,000 to 7,200 new respondents for each survey, document patterns of drug use in the specified populations at a given time.

A continuing survey of high school seniors, *Monitoring the Future,* uses a cohort-sequential, longitudinal design. A new cohort of high school seniors is surveyed each year, while a representative panel from each senior class is followed and examined over time. This enables one to discern antecedents from consequences of drug use, and to distingish changes due to cohort peculiarities and historical circumstances from those due to increased age. Initiated in 1975 by the Survey Research Center of the University of Michigan, *Monitoring the Future* annually surveys 16,000 high school seniors and 2,000 former students drawn, as panels, from each previous participating senior class. Results of the surveys are summarized in various NIDA reports as well as the IOM report, and include the following:

- Nearly a quarter of the total American population has used the drug, a 30-fold increase in use over the past 20 years.
- Of those who try the drug once, about one-half continue its use. Most users are adolescents and young adults who are regarded as potentially at high risk for damaging effects because of physiological and psychosocial immaturity.
- Age at first use has declined progressively over the last decade.
- The drug is readily available and much more potent than before. Potency has increased five-fold in the past five years.
- More than 1 in 10 high school seniors used marijuana 20 times per month or more at its peak use level in 1978. There is evidence that even four years after graduation nearly 9 out of 10 daily users continue use, half of them on a daily basis. Daily use among high school seniors is more common than daily alcohol use and is much more readily concealed.

Risk Determination

From the data presented above, NIDA staff concluded that marijuana use is a major health problem and that it causes both acute and chronic adverse effects. The stongest evidence for chronic adverse effects came from studies on the pulmonary system (with evidence from human studies supplemented by in vitro data) and the reproductive system (with the evidence almost entirely from animal studies). No quantitive estimate of the incidence of these adverse effects was developed because of limitations of the exposure information.

Chapter 4

AGENCY FOR TOXIC SUBSTANCES DISEASE REGISTRY

The Agency for Toxic Substances Disease Registry (ATSDR) is a separate, legislatively mandated Public Health Service (PHS) agency that works in close association with the Centers for Disease Control's (CDC) Center for Environmental Health (CEH) and is devoted to protecting the public health from the hazards of exposure to potentially toxic substances.

AGENCY OVERVIEW

Mandated under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (also known as CERCLA or "Superfund"), the agency for Toxic Substances and Disease Registry (ATSDR) was created by executive order of the Department of Health and Human Services (DHHS) Secretary in April 1983. The ATSDR conducts health assessments of hazardous waste sites, toxic emergency situations, and landfills and surface impoundments that may pose substantial potential risks to human health.

Mandate

The mission of ATSDR is to carry out the health-related responsibilities of CERCLA and the Resource Conservation and Recovery Act (RCRA), as amended, relating to CERCLA or RCRA eligible sites and substances found at those sites. The ATSDR works closely with local, state, and other federal agencies to reduce or eliminate illness, disability, and death resulting from exposure of the public and workers to toxic substances at spill and waste disposal sites.

To accomplish its mission, the ATSDR determines the extent of danger to the public health from a release or threat of release of a hazardous substance by conducting a health assessment of the situation; establishes and maintains disease and exposure registries; establishes and maintains an inventory of information on health effects of toxic substances; maintains a complete listing of areas restricted to the public because of toxic contamination; and coordinates the provision of medical care.

Organizational Placement

The ATSDR is an agency of the PHS. Much of its work is accomplished through interagency agreements with other PHS agencies. Its administrator also serves as the director of the CDC, and the assistant administrator is also the director of the CEH. Direct management of the agency is expected to be provided by the associate director, when this position is filled.

Agenda Setting

The identification and selection of topics of inquiry and evaluation of health hazards are determined by several mechanisms. Priorities are established primarily by requests for health assessments of hazardous waste sites for the Environmental Protection Agency (EPA) during its investigation process. Other requests for health assessments come from state or local health officials, private citizens, and other federal government agencies. When determining the agenda for health assessments, the administrator of the ATSDR gives priority to those sites or facilities where there is documented evidence of the release of toxic substances, where the potential risk to human health appears highest, and where, in the judgment of the administrator, the existing data are adequate to assess the potential risk to human health.

Other mechanisms for agenda setting are departmental initiatives derived from the knowledge, experience, and insight of the agency's staff and that of its closely allied organization, the CEH. Through the review of professional publications and the center's research findings and directions, its staff keeps abreast of the major issues related to hazardous chemicals. It establishes priorities that reflect contemporary problems for which the ATSDR is capable of providing credible resolutions. Such information shapes the agenda for research aimed at identifying and characterizing hazardous waste risks to the population.

Risk Assessment Methods

The ATSDR conducts two types of health risk assessments, although one type, the formal general risk assessment applicable to multiple sites, occurs rarely and only when not otherwise available. The more frequent type is the assessment of a particular site or situation. Both may use data from a variety of sources. The site-specific health or risk assessment uses, as much as possible, data related to that particular site (e.g., concentrations of hazardous substances, pathways, etc.), although formal or generic risk assessments are used where available and appropriate to the particular site. They may be modified if the assumptions needed for a formal risk assessment are not appropriate to the site or better data are available (e.g., if assumptions about adverse health effects in humans are not supported by studies of persons at the site).

The risk to human health is frequently expressed in qualitative terms of the imminent or significant nature or risk to the general public from a specific site. Consideration of the path of exposure to a population group is also discussed, with recommendations for limiting significant exposure. In some instances it is expressed as level of concern (e.g., 1 ppb), but risk may also be expressed as the excess number of cases that might be expected per population unit.

The steps performed, or reviewed where a formal risk assessment exists, are those of hazard identification, dose-response assessment, exposure assessment, and risk characterization. Other problems, issues, and limitations described in the introduction do, of course, enter into these health and risk assessments and decisions regarding them are made on the basis of the best available information and judgment, including that of consultants from outside the PHS where deemed necessary.

Scientific Review

Health risk assessments performed for or by the ATSDR receive careful scientific review from within the PHS and by outside experts in cases involving significant uncertainties or differences of opinion or the possibility of significant impact (e.g., dioxin). When information is to be published, it is generally submitted to peer-reviewed journals. In some cases the agency may solicit broad public review via notifications in the *Federal Register*.

Public Involvement

Public involvement takes either of two forms: (1) bringing hazardous waste problems to the attention of the ATSDR and (2) commenting on the results of ATSDR risk assessments. The former, which may have a substantial influence on ATSDR priorities, occurs mainly through municipal and state authorities (and occasionally through the news media) who identify hazardous waste issues and request assistance in determining their causes and in finding appropriate remedial options.

In relating its findings to local authorities, the ATSDR also provides opportunities for disclosure and discussion with the members of the affected communities through public forums generally convened by the EPA. Such forums provide an understanding of the scientific information and the means by which it was analyzed to draw inferences and conclusions related to specific environmental health issues.

Description of Risk Assessment Reports

Reports include a description of the data reviewed and methodology employed to make a final determination, and take the form of public health advisories, articles in *Morbidity and Mortality Weekly Reports* (MMWR), papers in scientific journals, and public announcements.

Mechanisms for Forwarding Results for Policy Decisions

The results of health risk assessments are routinely communicated by the ATSDR to the EPA and the states. In cases involving policy issues, significant impact, or expected controversy, results are elevated to the Assistant Secretary for Health (ASH) or Secretarial level for review.

Procedures for Disseminating Findings to the Public

The ATSDR disseminates its findings to the public through such vehicles as public health advisories (either directly or indirectly via the federal or state agencies that obtained ATSDR reports), reports to the EPA (that ultimately enter the public domain), MMWR and other scientific journals that are frequently abstracted by the news media, and direct mailings to interested citizens.

Evaluation of Public Health Effects of Assessments

The ATSDR obtains feedback from the EPA and the states and municipalities about the value of its reports and their use in action taken to ameliorate public health problems associated with hazardous wastes. In addition, the agency is constantly watchful of public reactions reported through the media. Finally, ATSDR and other PHS scientists are part of a network of professional contacts that provide an irreplaceable source of technical analysis and response. All of these resources serve as generalized tools for the fine tuning of subsequent analyses and their public dissemination, thereby strengthening the procedures and scientific bases for health risk assessments of the ATSDR.

Chapter 5

CENTERS FOR DISEASE CONTROL

The major goal for the Centers for Disease Control (CDC) is to lead public health efforts to prevent unnecessary disease, disability, and death. The CDC pursues this goal through prevention and control of infectious and chronic disease, and of disease, disability, and health associated with environmental and workplace hazards. Health risk assessments to identify and characterize health hazards are an integral part of CDC activities.

Four of the CDC's five centers, one institute, and three program offices are involved in health risk assessment activities; included in this group are the Center for Environmental Health (CEH), the Center for Infectious Diseases (CID), the Center for Health Promotion and Education (CHPE), the Center for Prevention Services (CPS), and the National Institute of Occupational Safety and Health (NIOSH). This chapter presents general procedures and policies related to the conduct of risk assessment, followed by examples of agency risk assessments that highlight the analytic processes involved.

AGENCY OVERVIEW

Risks from Exposure to Hazardous Substances: CEH

The Center for Environmental Health (CEH) was formed in January 1981 as part of a major reorganization of the CDC. The CEH conducts programs to assist in the surveillance, investigation, analysis, prevention, and control of environmentally induced health problems and chronic diseases.

Mandate

The CEH plans, directs, and coordinates a national program to maintain and improve the health of the American people by promoting a healthy environment and by preventing chronic diseases and noninfectious, nonoccupational, environmental and related factors that cause premature death and avoidable illness and disability. In carrying out this mission, the center conducts nonregulatory health risk assessments of various kinds, scope, complexity, and application.

Organizational Placement

As one of the cluster of five centers and one institute within the CDC, the CEH has a director who reports to the director of the CDC, and is organized into the following two components:

- *The Laboratory Component:* To measure substances in biologic (human) specimens; to measure the health effects of those substances in the biologic sample; to conduct a research and development program to accomplish these activities more efficiently and effectively; and to transfer appropriate technology to the states.
- *The Epidemiologic Component:* To identify adverse reproductive outcomes, childhood chronic diseases, and adult chronic diseases; to investigate potential causative environmental and related factors; to review exposure information and identify diseases and adverse health consequences in those exposed; and to study injury epidemiology and control strategies.

The CEH maintains liaison with other federal agencies, state agencies, and international health organizations, such as the International Program of Chemical Safety of the World Health Organization (WHO) and the various clearinghouses of the WHO, and gathers and analyzes epidemiologic information and other data relevant to the evaluation of environmental public health hazards. In performing its mission, the CEH works closely with the NIOSH, the Agency for Toxic Substances and Disease Registry (ATSDR), and other Public Health Service (PHS) agencies so that efforts in the occupational and nonoccupational settings are not duplicated. It frequently uses occupational data where exposure is generally more certain and of higher order in determining whether nonoccupational population studies should be done.

Agenda Setting

Agenda setting within the CEH is done within the general framework of its mission, and priorities of the Department of Health and Human Services (DHHS), the PHS, and the CDC. It is also responsive to special concerns of the Congress, the states, and the public. Other considerations are the extent to which there is a threat to the health of the public (seriousness of the threat, number of persons threatened) and the availability and effectiveness of interventions. In some cases the existence of interagency or other agreements determines priorities.

Risk Assessment Methods

CEH risk assessments vary greatly in their scope, complexity, and application. They range from formal generic quantitative risk assessments to site-specific health or risk assessments that combine existing hazard characterizations with exposure data specific to the site in question. In certain settings, health risk assessments relying wholly or in large part on qualitative information are not unusual. The more complex the situation and the greater the uncertainties, the more general and the more qualitative the manner of stating the risk is likely to be.

While risk assessment definitions in general use are likely to have been formulated with toxic substances or perhaps radiation in mind, the same approach and logic are involved in any kind of risk assessment: identification of a hazard and the related adverse health outcome(s); determination of the quantitative relationship, if any, between the two; identification of real or theoretical exposures; description of the actual or potential risk that has, is, or may occur; and, finally, some qualitative or quantitative expression of that risk for use in preventing future potential exposures and in eliminating, controlling, or taking other action related to a known or suspected risk.

The CEH is concerned with each of these steps as applied to unintentional injuries, chronic diseases, adverse reproductive outcomes, and other adverse health outcomes caused by nonoccupational, noninfectious, environmental hazards, which include toxic substances (manmade and naturally occurring), ionizing radiation, weather phenomena (heat, cold, tornadoes), and the physical environment (leading to injuries). The CEH is also involved with developing the technology needed to conduct such work (e.g., laboratory techniques and procedures to measure body burdens of chemicals in order to determine actual human exposures). Activities contributing directly or indirectly to risk assessment include performing or supporting surveillance, health studies, health consultations, and health assessments; establishing and maintaining exposure and health outcome registries; designing and implementing interventions; developing technology; conducting training; and developing state capacity.

A considerable amount of CEH activity related to risk assessment is done under interagency agreement with other agencies, e.g., superfund-related activities under agreement with the ATSDR. The CEH maintains several monitoring and surveillance systems such as the Birth Defects Monitoring System that are often instrumental in identifying potential hazards and in generating hypotheses for planning and conducting detailed epidemiologic studies to determine such statistics as the incidence and causes of very low birth weights of infants living near hazardous substance waste dumps. Much of the information used for hazard identification and dose-response assessments in such studies would be derived from other sources. Although the CEH does virtually no animal toxicologic studies, it does contribute information from laboratory and epidemiologic studies for use in risk assessments. CEH has no direct regulatory responsibilities but frequently provides information to other agencies such as the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) that do have such responsibilities.

Scientific Review

CEH health risk assessments are carefully reviewed by the scientific staff before release outside of the CDC. Depending on the nature of the assessment and its intended use, it may be further reviewed by other CDC staff, staff of other PHS agencies, other government agencies, state personnel, and scientists from academia and industry. In some cases, the center may solicit broad public review via notification in the *Federal Register*. The decision regarding the level of review rests with the directors of the CEH and the CDC.

Public Involvement

Public involvement takes two forms: bringing environmental problems or potential problems to the attention of the center, mainly through local and state authorities and commenting on the center's health risk assessments.

As part of the process of relating the results of health risk assessments to state and local authorities, opportunities for disclosure and discussion with members of affected or potentially affected populations and communities are provided frequently through public meetings and forums. Such forums allow the public to gain an understanding of the scientific conclusions reached in a particular instance and the means of analyses and inferences and conclusions reached. When a health assessment seems to be particularly sensitive or controversial, the CEH will seek public involvement and comment by placing notifications in the *Federal Register*.

Description of Risk Assessment Reports

Health risk assessment reports take the form of public health advisories to state authorities and to the EPA, articles in the *Morbidity and Mortality Weekly Report (MMWR)*, papers in scientific journals, and public announcements. While articles and papers usually describe each step of the assessment, health advisories and public announcements usually contain only the conclusions and recommendations, if any. Final reports generally reflect reviewers' comments; however, emergency advisories, because of their very nature, will generally not have benefited from such review. Some reports may discuss the health implications of risk management options.

Mechanisms for Forwarding Results for Policy Decisions

The level of policy review received by a health risk assessment depends on the degree to which it departs from usual policy, its sensitivity, and its potential for being controversial. Although assessments are not generally reviewed beyond the center level, on occasion they may be reviewed by the director of the CDC, the assistant secretary for health of the PHS, and in rare instances the secretary of the DHHS. Such reviews more frequently take the form of a briefing than a statement of decision.

Procedures for Disseminating Findings to the Public

The CEH disseminates the results of health risk assessments through such mechanisms as public health advisories, reports of various types, articles in the *MMWR*, papers in scientific journals, and responses to inquiries from the news media.

Evaluation of Public Health Effects of Assessments

The CEH obtains and receives both formal and informal evaluation information for its health risk assessments from a variety of sources, including other federal agencies, state and local government organizations, industry, academic and other scientists, and the public. Whether it deals with process or content, the information received is seriously considered as the CEH revises its risk assessments, formulates subsequent assessments and policies, and determines procedures.

Risks from Exposure to Infectious Agents: CID

The mission of the Center for Infectious Diseases (CID), one of the centers within the CDC, is to prevent unnecessary infectious disease morbidity and mortality. The CID focuses on surveillance of infectious disease occurrence, disability, and death; epidemic investigations; epidemiologic field research; and laboratory studies. Although the CID is profiled in this section relating risk assessment and infectious agents, another CDC center—the Center for Prevention Services (CPS)—is also involved. The mission of the CPS is to administer national assistance programs involving preventive health services to state and local health agencies. Since these programs include both infectious and chronic diseases, the CID and the CPS are closely coordinted on a daily basis in many activities. The programmatic areas of overlapping responsibility include vaccine-preventable diseases, sexually transmitted diseases, and tuberculosis.

Mandate

The overall goal of the CID is the development of methods of preventing unnecessary morbidity and mortality due to infectious disease. Through program activities and research related to the diagnosis, prevention, and control of infectious diseases, it seeks to achieve this goal. The CID activities most directly related to risk assessment involve applied research on infectious disease cause and prevention.

Organizational Placement

The CID is composed of three program offices and six divisions. Program offices deal with biological products, hospital infections, and laboratory research on sexually transmitted diseases. Divisions include the Division of Bacterial Diseases, the Division of Host Factors, the Division of Mycotic Diseases, the Division of Parasitic Diseases, the Division of Vector Borne Viral Diseases, and the Division of Viral Diseases.

Agenda Setting

The allocation of CID resources requires that priorities be set in terms of the types of infectious diseases that are investigated. The following criteria are considered in setting priorities for work on a particular disease:

- Overall incidence or magnitude of the disease;
- Severity of disease, including incidence of death;
- Likelihood that the disease is preventable; and
- Degree of medical knowledge concerning the disease.

Each point is implicitly or explicitly addressed in the formulation of an appropriate response. Sometimes, however, there is little or no information on these factors; thus decisions about program directions must be based on the collective judgments of the CID director and his immediate staff. For certain specific issues, higher-level officials (including the director of the CDC) become involved in the normal planning process.

Risk Assessment Methods

Identification of disease-related hazards, the initial step in risk assessment, takes place through surveillance programs, laboratory research, epidemiologic field studies, and epidemic investigations. Each of these activities provides a different kind of information and perspective from which to study potential risks. Many disease-related hazards are brought to the attention of CID staff through requests for epidemic investigations and surveillance. Reporting systems maintained by the CID, except for a few, such as the National Nosocomial (hospital-acquired) Infections Surveillance System, generally gather information on disease incidence reported to state health departments. The CID may also obtain reports directly from local health departments, physicians, or individual citizens. As a matter of policy, urgent information on outbreaks is immediately shared with states, while surveillance data are periodically analyzed and then shared. The *MMWR* often communicates this information.

In hazard characterization, the main methods used are epidemiologic investigations of possible sources, modes of spread, and host factors involved in outbreaks caused by particular agents. However, epidemiologic studies may also be supplemented by dose-response and mechanistic studies in animals and in vitro systems. After a causative agent has been identified and diagnostic tests developed and applied, risk factors (e.g., sources, modes of spread, host factors) can be more clearly defined, as in the cases of risk associated with AIDS and hepatitis B virus infections.

Risk determinations are often based on attributable risk or relative risk. After the CID identified toxic shock syndrome (TSS) as an illness primarily affecting women of menstrual age, epidemiologic studies associated tampon use with an increased risk of the disease, and later identified a specific tampon brand as being associated with a substantially higher risk than others. Further studies initiated by the CID found that the presence of strains of *Staphylococcus aureus* producing TSS toxin were required for tampon-associated and other forms of the disease to occur.

In the case of immunization programs, formal risk determinations often involve the Advisory Committee on Immunization Practices (ACIP). The ACIP meets regularly at CDC to review immunization practices and activities in the United States and elsewhere often using CDC data on outbreaks of immunizable diseases and from field studies of vaccine efficacy in these deliberations. Topics of concern to the ACIP have included vaccines for hepatitis B, influenza, measles, rabies, and pertussis.

Scientific Review

Circumstances determine the type and extent of scientific review at the CID. The time scale and point at which decisions are made are necessarily different for an imminent health problem and for long-term studies. In the case of the first recognized outbreak of legionellosis (Legionnaire's disease), for example, a review of the available information and likely diagnosis was initially conducted internally by CDC staff with the involvement of persons in the CDC director's office. In such cases, the internal view is often supplemented by external telephone consultation with public health officials, infectious disease experts, including former CDC officers, and other outside consultants who can help review clinical and laboratory features of cases, case definitions, estimates of risk, and other important aspects of the case at hand. The findings concerning etiologic agents and the clinical and epidemiologic characteristics of the disease are announced to the scientific community and the public in accord with the public health urgency of the findings. Serious outbreaks of unknown cause are described on an urgent basis in the *MMWR*.

Risk assessments derived from long-term epidemiological studies or laboratory work are also reviewed internally; however, the findings are more likely to be reported in the form of a scientific paper presented at a scientific meeting and published for a peer-reviewed medical journal. Thus, before the published findings are made available in the medical literature, the study and its conclusion will have undergone both an internal and an independent external review. Once published, the study is open for review and comment by the entire medical community.

When a risk assessment has particularly significant or sensitive health implications (e.g., AIDS), the CDC may supplement these review mechanisms with review by an internal special task force or a panel of outside consultants. Other government agencies may also request an opportunity to review and possibly reanalyze available information in such cases.

Public Involvement

State and local health agencies are important collaborators with the CDC and also act as intermediaries between the CID and the public. State and local health agencies are responsible for reporting disease incidence, new disease outbreaks, and other measures associated with hazard identification. Individuals also report cases directly to the CID, however, and the public has considerable input throughout the process of determining risk and in the eventual reduction of risk through preventive measures. Public involvement is important because behavioral changes in the population may help reduce risks of acquiring specific infections, such as AIDS.

Description of Risk Assessment Reports

Generally, the CID prepares three types of reports in the course of investigating the risks associated with outbreaks carried by an infectious disease agent. The first report, usually one page in length, is an internal CDC document issued shortly after the CID becomes involved, which simply describes the disease outbreak and the type of investigation to be performed by the CID. The second report, a letter to the state health department, is usually several pages in length, and describes the preliminary results of the investigation. Where applicable, it also presents descriptive findings of the clinical course of the disease, epidemiologic investigation, and environmental survey. Conclusions and recommendations follow with supporting data. The third report is similar to the second but is more complete, based on additional data that may be collected over the course of a year or more. It explains the methods of the investigation, which may include analysis of data such as clinical contact reports, epidemiologic investigation, environmental survey, and laboratory tests. It also presents the results of the investigation, followed by a discussion, conclusions, and recommendations. Although these reports are considered to be for administrative use and not for publication, the information of substantial public health importance contained in these reports is routinely published in the *MMWR*. Other types of "risk assessment reports" include articles in the *MMWR*, manuscripts, manuals, and memos to state and territorial health departments.

Mechanisms for Forwarding Results for Policy Decisions

Assessments of investigations of outbreaks are sent, as appropriate, to the director of the CDC, high-level officials within the PHS and state health departments, and Epidemic Intelligence Service officers (CDC staff placed in state public health agencies). Reports of outbreak investigations and long-term studies and their public health implications are forwarded in a similar manner. The documents are sent from the director of the CID to the director of the CDC, who transmits them to key officials in the PHS and state health departments.

Procedures for Disseminating Findings to the Public

The *MMWR*, CDC's major publication, is the primary vehicle for disseminating the results of risk assessments. The conclusions of long-term epidemiologic studies, vaccine studies, and other assessments of risk are regularly published in medical journals and the *MMWR*. Because the *MMWR* is published weekly and is read widely by physicians and other health officials, it provides an effective means for distributing information quickly. The lay public is often informed through the mass media, which regularly review the *MMWR*.

The CID sometimes takes more direct steps. When an infectious disease appears to present an immediate hazard to a localized region, for example, the CID will focus its information dissemination efforts on that area. In addition to the usual procedure of transmitting risk assessment information to officials in state health departments, key officials from local health departments and hospitals may be notified directly.

Evaluation of the Public Health Effects of Assessments

Continual monitoring and follow-up activities are important functions of CID's surveillance systems. After the CID completed studies on the epidemiology of hepatitis B in high-risk groups in the United States, it continued long-term follow-up of participants in the hepatitis B virus vaccine trial in order to better define and update recommendations for vaccine use. As a result of another study, the CID has estimated that its recommendations for surveillance and control of nosocomial (hospital-acquired) infections are able to reduce the incidence of such infections by at least 20 percent. Other follow-up efforts include surveillance of influenza, legionellosis, and pneumococcal disease, which may be useful in identifying new problems and in assessing the effectiveness of control measures.

Risks Associated with Lifestyle: CHPE

The Center for Health Promotion and Education (CHPE) is one of the group of five operational centers and one institute within the CDC. Recognizing that knowledge, attitudes, and behavior are complex etiologic agents of many of today's public health problems, the center uses innovative approaches to public health issues related to nutrition, human reproduction, personal violence, and lifestyle-related risk factors (smoking, alcohol abuse, hypertension, obesity, lack of exercise, and stress) leading to major chronic and preventable conditions. The major foci of risk assessment activities at the CHPE are the identification and characterization of behavioral factors ("lifestyle") that affect health risks.

Mandate

The mission of the CHPE is to plan, direct, and coordinate a national program for the development, stimulation, and support of health promotion, health education, and risk reduction activities. To meet these goals, the CHPE conducts research, maintains surveillance systems, assists state and local agencies in establishing programs, and provides technical assistance both nationally and internationally. Thus, both risk assessment and risk management activities are central components of CHPE's mission.

The CHPE was established as the result of the October 14, 1980, reorganization of the CDC (45 *Federal Register* 67772-73), which placed in the CHPE three existing CDC components concerned with health conditions related to personal lifestyle choices that may be addressed through public and professional education: health education, nutrition education, and family planning evaluation. One of these, the former Bureau of Health Education, was originally established in 1974 as a result of recommendations of two groups (the President's Committee on Health Education and the PHS Task Force on Health Education) that there be a federal focus for health education activities. The CHPE's nutrition and reproductive health responsibilities redefined the functions of CDC units responsible for nutrition surveillance and family planning evaluation.

Because violence is a serious public health problem, the CHPE initiated a violence epidemiology initiative in 1980 as part of its Special Projects activity of the office of the director. In 1983, this initiative was formally established as the Violence Epidemiology Branch. The Educational Resources Branch, established in 1980 to provide technical services to disseminate information developed by the CHPE, also gained branch status in 1983.

Organizational Placement

Risk assessment activities are conducted by the CHPE's three divisions—Division of Health Education, Division of Reproductive Health, and Division of Nutrition—and two branches within the office of the director—Violence Epidemiology Branch and Educational Resources Branch. Each division of the CHPE has several branches, with at least one branch in each division responsible for developing research procedures and collecting, analyzing, and interpreting data. Each division also has a field services branch responsible for contacts with national, state, and local agencies as well as international organizations and agencies. Because of their surveillance activities, both the Division of Reproductive Health and Division of Nutrition have statistics branches responsible for the collection and manipulation of data. The Violence Epidemiology Branch and the Educational Resources Branch are not subdivided.

Agenda Setting

In setting the agenda for its work on health problems related to nutrition, human reproduction, violence, and lifestyle-related risk factors, the CHPE is guided foremost by the "1990 Objectives for the Nation, the Recommendations for a National Strategy for Disease Prevention: A Report to the Director, CDC," published June 30, 1978; and the recent CDC staff conference (the Unicoi Conference) to establish health problem priorities. Priorities are determined by the CHPE in light of congressional mandates, departmental objectives, PHS objectives, CDC objectives, and requests for assistance from federal, state, local, and international agencies. Decisions on small projects are usually made by division directors in consultation with division staff, while larger projects are discussed and decided on by the appropriate division leaders in consultation with the CHPE director's office. To support its research agenda for high-priority topics, CHPE generates formally prepared issue papers that incorporate state-of-the-art reviews by leading nongovernmental experts and consultations with users of CHPE technical assistance. In 1984-85, this process was applied to exercise and physical fitness, violence, and surveillance of low birthweight-related infant mortality.

Risk Assessment Methods

The major risk identification techniques used by the CHPE are surveillance studies and prevalence surveys, including:

- *Behavioral Risk Factor Prevalence Surveys*. The CHPE has developed a system for state health departments to use in ongoing telephone surveys of the general public that monitor changes in behavioral risk factors (such as sedentary lifestyle, lack of seatbelt use, smoking, alcohol misuse, uncontrolled hypertension, and obesity).
- *Puerto Rico Fertility and Family Planning Assessment*. The Division of Reproductive Health has assisted the Commonwealth of Puerto Rico in a multipurpose survey to obtain relevant baseline data for assessing the acceptability of and need for family planning and maternal and child health services in Puerto Rico and to ascertain how the high use of

female sterilization in Puerto Rico has affected its demographic profile.

- *Nutrition Surveillance.* The Division of Nutrition receives information from 35 states on selected indices of nutritional status. These data are analyzed and published in annual Nutrition Surveillance Reports.
- *Suicide Surveillance.* The Violence Epidemiology Branch is developing a suicide surveillance system that will assess trends and risk factors, identify suicide clusters, and yield information that could be used to monitor the effectiveness of suicide prevention programs.

Other CHPE systems—Homicide Surveillance, Ectopic Pregnancy Surveillance, Teenage Pregnancy and Fertility Surveillance, Sterilization Surveillance, and Maternal Mortality Surveillance—identify groups at risk and assess factors that increase or decrease risk. Research activities include:

- *Study of Cancer and Steriod Hormones (CASH).* This is the largest case-control study of the association of oral contraceptive use and the risk of breast, endometrial, and ovarian cancer.
- *Collaborative Review of Sterilization (CREST).* This is a multicenter, prospective study to assess the safety (early and late complications) and efficacy of tubal sterilization.
- *Exercise and Health.* A cohort study of the Division of Health Education examined the incidence of injuries and benefits among runners of the Annual Peachtree Road Race.

Exposure characterization is carried out in conjunction with hazard identification, since surveillance studies and prevalence surveys also indicate what proportion of a population is exposed to a given health factor and to what extent it is exposed. The Behavioral Risk Factor Prevalence Surveys being conducted through state health departments are the primary mechanisms by which individual states and the CHPE determine prevalence of lifestyle-related risk factors.

At the CHPE, risk identification, risk characterization, and exposure characterization all include in-depth reviews of available data and literature. Outside experts often assist CHPE scientists, as in September 1984, when the CHPE convened a group of 15 experts to a "Workshop on the Epidemiologic and Public Health Aspects of Physical Activity and Exercise." The discussions at this workshop were used by the CHPE to set its 1985-86 research priorities.

Scientific Review

Before a report is released or a manuscript is published as a journal article, it receives an extensive internal review at the CHPE. Early stages of this review process consist of informal review within the division. Once the final draft of a manuscript is prepared, the author's branch chief and division director must review and acknowledge clearance of it, and all recommendations and comments are considered. The manuscript then goes to the Educational Resources Branch where it is edited and transmitted to the CHPE director or his designate (assistant director for science), who is the ultimate clearance authority for the center. If the director determines that independent review is needed to support the internal review findings, external review is sought from other CDC components, individual non-CDC expert consultants, or both.

Public Involvement

Substantial public input comes indirectly to the CHPE when state and local health departments request technical assistance in dealing with issues of public concern. From time to time the CHPE sponsors national meetings of state directors of programs in health education, nutrition, and family planning, to identify program needs and to exchange information on these areas of health problems.

When the CHPE works on projects with specific relevance to particular communities or target populations, meetings may be held with community representatives to help identify major public concerns. The Division of Health Education's Community Training Modules are designed to generate community organization and involvement in health education.

Description of Risk Assessment Reports

The CHPE publishes its findings in a variety of forms, depending on the subject nature and target audience of the information to be transmitted. The CHPE articles are published in scientific journals and in the *MMWR;* the CHPE also publishes articles in quarterly surveillance reports, surveillance reports, individual project reports, and two publications: *Focal Points* and *Current Awareness in Health Education*. CHPE manuscripts and reports are scientifically oriented and include thorough descriptions of methods used, analysis performed, and results and conclusions reached. Synopses of research reports are often published in the *MMWR*.

Mechanisms for Forwarding Results for Policy Decisions

The CHPE disseminates its internally published research reports through its scientific, medical, and education networks as well as to other departmental components and relevant federal agencies. Recipients include personnel in state health and education departments, DHHS regional offices, voluntary health agencies, libraries and information centers, family planning clinics, and local health departments. A recent example is an annotated bibliography on the prevention of injuries in the elderly. This document serves as a resource both for the field and for the Public Health Service–Administration on Aging (PHS-AOA) joint initiative on injury prevention, and is being disseminated through the CDC and the AOA channels.

States typically receive reports of the CHPE's findings, which they may use to develop policy and set objectives. A variety of ad hoc and formal mechanisms are used for policy-relevant findings of surveillance and epidemiologic investigations. The former include oral briefings of the CDC director and action memoranda with recommendations; the latter include program reviews and planning/budgeting cycles, such as option papers for the Office of the Assistant Secretary of Health (OASH) to use in planning for risk reduction.

Procedures for Disseminating Findings to the Public

Copies of published reports are generally available to the public through the National Technical Information Service (NTIS). Other CHPE publications, such as the periodicals *Focal Points* and *Current Awareness in Health Education*, are sold by the U.S. Government Printing Office.

CHPE findings that result from federal, state, local, or international requests for assistance are reported directly to the initiator of the request and to a project's funding group(s). Most of CHPE's research is either reported in the scientific literature or in the form of government reports. While the *MMWR* is primarily used to reach health professionals, its findings are also widely reported in the news media.

In January 1985 the CHPE's health education database, which includes journal articles, reports, monographs, and program descriptions, and contains CHPE-produced items relevant to health education methodology, became available for interactive searching nationally and internationally. Although the primary audience is health and education practitioners, the public has access to the database as well.

Evaluation of Public Health Effects of Assessments

The CHPE provides technical assistance to a variety of state programs, including family planning programs, nutrition programs, and school health programs, and to communities undertaking risk reduction programs. There is no formal mechanism to determine the effects of its research and technical assistance, but when CHPE-developed or recommended programs are implemented, changes in risk can be reviewed by monitoring changes in the surveillance data that CHPE collects. The Behavioral Risk Factor Prevalence Surveys offer a mechanism for measuring effectiveness of programs implemented in response to the CHPE's Health Education Community Training Modules that were being initiated in several communities in 1985. With CDC and state health agency assistance, local communities are also using this survey method to establish priorities and assess needs.

There are some methodological limits on evaluating the effectiveness of the CHPE's activities, including: (1) the length of time between CHPE effort and adoption of public or professional practices, (2) the multiple causes of change and the inability to determine how much change should be attributed to each, (3) the high cost of rigorous evaluation, and (4) the need to examine the impact of the CHPE's activities in the context of overall state and local programs not under CDC control.

Risks Associated with the Workplace: NIOSH

The National Institute for Occupational Safety and Health (NIOSH), a component of the CDC, was established by the Occupational Safety and Health Act of 1970 (Public Law 91-596) to conduct research, experiments, and demonstrations relating to occupational safety and health, including studies of psychological approaches for dealing with occupational safety and health problems. The NIOSH uses the results of these activities to produce criteria dealing with toxic materials and harmful physical agents and substances. The criteria describe exposure levels that are safe for various periods of employment, including but not limited to the exposure levels (if any) at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his or her work experience. The 1977 Mine Safety and Health Act (Public Law 95-164) contains similar language.

The Occupational Safety and Health Act prescribes a number of other activities to be conducted by the institute, including, but not limited to, surveillance of the workplace and the conduct of industrywide studies. The NIOSH also performs research to determine the biomedical and behavioral effects of exposure to toxic materials and harmful physical agents.

The activities of the NIOSH provide information that is used to assess and describe the nature and extent of exposures in the workplace. The same information enables the director of the NIOSH to formulate recommendations for workplace standards, which are forwarded to the Secretary of Labor for consideration in promulgating new standards.

The NIOSH produces several publications that involve health risk assessment. Criteria documents are detailed, comprehensive reviews of all available information on selected occupational hazards and include recommended standards that may be promulgated by the Mine Safety and Health Administration (MSHA) or the Occupational Safety and Health Administration (OSHA). Current intelligence bulletins contain brief reviews of new information on possible hazards. Health hazard evaluations (HHEs) present the results of investigations that characterize workplaces and identify potential risks presented by exposures to chemical, biological, or physical agents. These latter documents and other NIOSH reports may be used as guides for controlling similar hazards in other workplaces, and may also be used as sources of data for criteria to set standards.

Mandate

The Occupational Safety and Health Act of 1970 (Public Law 91-596) and the federal Mine Safety and Health Act (Public Law 95-164) authorize the NIOSH to develop occupational safety and health standards and to support research and experiments necessary to develop criteria to improve occupational safety and health standards. Section 20(a)(3) states specifically that the DHHS Secretary is to develop criteria dealing with exposure to harmful substances and agents so that employee exposures will be safe, while Section 20(a)(5) provides the Secretary, working through the

NIOSH, with the authority to require employers to measure and report on the exposure of employees to potentially harmful conditions and to establish programs of medical examinations and tests to help detect problems.

The institute recommends standards and improvements to existing standards to the OSHA and the MSHA through a variety of means, including criteria documents, direct testimony during Department of Labor rulemaking, congressional testimony, and publication of current intelligence bulletins.

HHEs are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, which requires the Secretary to publish each year a list of all known toxic substances and their toxic concentrations. The act also requires the NIOSH to respond in a timely manner to reports of potentially hazardous exposures in a workplace and to develop an appropriate criteria document if the need exists. An important part of the charge is its mandate to conduct research necessary to develop criteria for new and improved occupational safety and health standards, and to forward any resultant recommendations to the secretary of labor. As part of a special mandate to collect, compile, and analyze occupational safety and health statistics, and statistics on disabling or significant injuries and illnesses, Section 24(a) authorizes the NIOSH to conduct a program of grants to states, localities, and academic centers.

Organizational Placement

The NIOSH staff within all three branches of the Division of Standards Development and Technology Transfer (DSDTT) participate in the production of criteria documents. Although there is currently limited in-house expertise in quantitative risk assessment, the NIOSH is developing such expertise and expanding its capability to conduct these assessments. Current intelligence bulletins are usually produced by DSDTT staff, primarily within the Document Development Branch. One quantitative cancer risk assessment, however, was prepared by a contractor to DSDTT. Occasionally, bulletins may be prepared by staff from other NIOSH divisions that have expertise in certain hazardous materials or processes.

HHEs are performed by medical, nursing, and industrial hygiene technical staff of the Hazard Evaluations and Technical Assistance (HETA) Branch of the Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS). The HETA occasionally receives assistance from other NIOSH staff, or from medical service contractors such as dermatologists or pulmonary physicians.

Agenda Setting

The list of substances, processes, and other hazards for which criteria documents are to be developed in a given fiscal year is determined approximately one year in advance. Since 1972, the NIOSH has completed more than 110 criteria documents. The NIOSH solicits nominations for criteria documents from NIOSH divisions; the OSHA and other government agencies, such as the MSHA, the EPA, the National Cancer Institute (NCI), and the National Institute for Environmental Health Sciences (NIEHS); industry and trade associations; labor and union groups; public interest groups; and members of the scientific community. The nominations to date have been generated from a variety of sources, including NIOSH divisions as well as the Department of Labor.

In evaluating the nominations for criteria documents, DSDTT staff decide whether there is a need for a recommended standard for each nominated hazard, whether there is sufficient information with which to justify a recommendation for a standard, and, if not, what additional research is needed before development of a standard can be recommended. Accepted nominations are ranked according to the number of potentially exposed workers, magnitude of each exposure, type and severity of adverse health effects, potential for producing chronic or irreversible effects such as cancer or reproductive effects, gaps in information, and future trends in use or application of the substances or processes. Although the choice of priorities rests in large part on the professional judgments of senior NIOSH staff, including institute management staff, the final decision rests with the NIOSH director.

Subjects for current intelligence bulletins are proposed by DSDTT staff after analysis of current information. On the basis of the type and potential severity of the hazard, the number of workers exposed, and the need for a timely report on the hazard (pending changes in use or application, discovery of previously unknown effects, etc.), subjects are selected for document development. Over 40 bulletins have been issued since 1975.

The Division of Safety Research (DSR) prepares reports that include technical guidelines. Saftey topics come to the attention of the DSR through analysis of injury statistics derived from a wide range of data bases, site evaluations of fatal accidents, health hazard evaluations, and communication with other government agencies and representatives of industry and labor. The DSR looks specifically for high-risk industries, such as grain handling (see below); high-risk occupations in a particular industry, such as roofing in the construction industry; and such frequent injuries as back injuries. Once a problem area has been identified, the DSR determines whether, considering its resources, the magnitude of the problem, and its amenability to prevention, the division can effectively address the issue. Potential topics are also weighted according to the severity of and degree of exposure to the hazard involved. The director of the NIOSH makes final decisions on topics to be developed in DSR reports.

The HETA branch of the NIOSH conducts over 500 field investigations per year of possible health hazards in the workplace. These requests result in (1) an evaluation of whether hazardous chemical, biological, or physical agents are used or found in the workplace; (2) recommendations for control procedures and improved work practices to reduce exposure levels and subsequent health effects; and (3) recommendations for medical screening to determine the effectiveness of existing or new controls in the workplace.

The activities undertaken by the HETA branch are assigned high- or low-priority status, but within these categories they are usually performed in the order in which requests are received. Low-priority investigations include compliance-oriented evaluations, investigations intended only to provide evidence for worker's compensation actions, routine monitoring, previously evaluated occupational exposures, and investigations of common occupational health problems with routine solutions. High-priority investigations are those involving health complaints or illness, poorly documented or previously unrecognized effects of common exposures, new exposures or processes, and/or exposures and adverse health effects within occupational groups not previously evaluated.

The HHE program also responds to current research interests of other NIOSH programs, and may provide data for programs in other divisions within the institute, for NIOSH research projects and documents, and as a follow-up on the findings of NIOSH/NTP toxicology studies.

Risk Assessment Methods

Criteria documents provide critical evaluation of information found in the literature pertaining to the hazard studied, assessing the data first for relevance to the workplace environment, then for quality. In evaluating the possible adverse effects of a substance, the NIOSH places emphasis on epidemiologic data and exposure data derived from its own surveillance programs, published epidemiology data from all sources, and case studies and clinical evaluations. A large amount of information on these subjects is obtained from NIOSHSTIC, NIOSH's on-line bibliographic information retrieval system.

In the absence of data that relate human exposure to adverse health effects, NIOSH staff rely on animal data to identify potential adverse health effects. Animal studies must mimic known routes and extents of human exposure or provide insight into the absorption, excretion, and metabolism of the substance. Since in most instances, the exposure route of primary concern is inhalation, animal inhalation studies are those of greatest interest. Experimental protocols of lifetime animal studies in both sexes are reviewed in accordance with National Toxicology Program (NTP) guidelines, as well as in vitro tests using microorganisms.

To ensure a complete and critical evaluation of published in vivo and in vitro studies, the DSDTT has developed a standard format for a technical evaluation data sheet intended for use only as a broad guide for data analysis. Interpretations of the data or predictions of dose-response relations from the data are accompanied by an explanation of any assumptions used to make these interpretations or predictions, as well as estimates of the number of workers potentially at risk in various exposure categories.

The analysis of information embodied in criteria documents integrates all of the information on the toxicity of the substance(s) evaluated and presents conclusions concerning possible adverse effects in workers. For noncarcinogens and carcinogens, the correlation of exposure and effect is made. Because the NIOSH has not always performed quantitative cancer risk determinations in the context of criteria document development, however, precise mathematical estimates of risk to the exposed worker population were sometimes not included for carcinogens. The Document Development Branch relies on continual searches of the scientific literature for new information on potential or recognized occupational hazards.

The technical guidelines developed by the DSR are critical evaluations, similar to criteria documents, of all available evidence pertaining to the selected hazard. Once a safety topic comes to the attention of the DSR, it is evaluated and specific hazards are identified through analysis of accident reports to determine the cause of accidents and what safety measures might have prevented them. To obtain as much information as possible on a topic, the DSR also conducts literature searches and facility visits, and consults experts from industry, labor, government, and the academic community.

In the exposure characterization phase of the assessment, exposure rates are calculated from available data on the distribution of the workforce, occupations at risk, and particular facilities, and analyzed with respect to the distribution of injuries. All data used for hazard identification, hazard characterization, and exposure characterization are evaluated for validity and the degree of confidence that can be placed in them, and are weighted accordingly.

Based upon their findings, the DSR determines the relative risks of safety hazards and what safety measures can be implemented to prevent them. The DSR then makes a list of safety recommendations and ranks them, under the assumption that no one has the resources to implement all safety recommendations, but will implement those that are most efficient in terms of worker safety and economy.

Formal HHE reports are produced for only about half (about 250) of the investigations of suspected hazards performed each year. In general, written reports are prepared for those investigations involving more serious occupational health problems and for those situations requiring more comprehensive investigations. The degree of detail and formality in written evaluations depends on the characteristics of the suspected hazard, level of worker exposure, severity of health effects, amount of information available through previous investigations of similar hazards, and type of information requested by the employer/employees. Written evaluations usually attempt to:

- Collect medical/epidemiological information on the affected workers;
- Review the literature for reports of adverse effects associated with the substances/physical agents in the workplace;
- Collect information on workplace exposures to possibly hazardous substances/agents;
- Compare exposures likely to occur in the workplace with exposures cited in reports of adverse effects in humans and/or animals; and
- Reach conclusions for these data concerning adverse effects that may be related to exposures at the workplace.

For certain toxic end points, special medical surveillence methods may be employed. In the case of possibly carcinogenic or mutagenic materials, special studies (e.g., cytogenetic studies, tests for sister chromatid exchange and urinary mutagenesis, and reproductive-related studies such as sperm abnormality tests) may be performed in conjunction with the NIOSH Divisions of Biomedical and Behavioral Sciences or Respiratory Disease Studies. The NIOSH may use a consultant to provide information in areas where there is no expertise within the institute.

Scientific Review

The first complete draft of a criteria document is reviewed by the senior review staff of DSDTT. After approval of the director of the DSDTT a revised draft is submitted to external reviewers who have an interest in the control of occupational or environmental hazards. Some of the reviewers are affiliated with other federal agencies (the EPA, the OSHA, and the MSHA), trade associations, and labor groups; others are individual occupational safety and health professionals (whose advice does not necessarily represent that of the organization for which the individual works). Persons from industry who were interviewed to provide data or information for the document are invited to review the report for technical accuracy. The NIOSH also invites professional societies such as the American Industrial Hygiene Association, the American Academy of Occupational Medicine, the Society of Toxicology, and the American Association of Occupational Health Nurses to review draft criteria documents.

After comments of external reviewers are considered for incorporation into the document, a final draft is prepared, and the office of the director of the NIOSH performs a final evaluation. Although the NIOSH may reject a reviewer's criticisms, present NIOSH policy requires that each reviewer be informed in writing of the rationale for the institute's response to each comment.

Current intelligence bulletins are produced in only three to six months for the purpose of disseminating new scientific information about occupational hazards. Drafts are reviewed internally in a manner similar to that used for criteria documents.

HHE reports are reviewed by staff of the Hazard Evaluations and Technical Assistance Branch and by the office of the division director before publication. Comments and suggestions may be solicited from other branches within the Division of Surveillance, Hazard Evaluations, and Field Studies, or from members of other NIOSH divisions. Before they are sent to OSHA, all final HHE reports are reviewed by the affected employers and employees to eliminate trade secrets and other proprietary information.

Public Involvement

The public may be involved at various stages in the process of developing NIOSH policy statements. For example, during the preparation of criteria documents, individuals may submit nominations, provide information and data for evaluation (especially at times when NIOSH staff members visit work sites to obtain information about manufacturing or use of the substance or process), or aid in reviewing the draft document as members of an external expert advisory review group. In addition, persons who were contacted at the work sites are invited to check the accuracy of the reports.

Before any major study is conducted, the study protocol receives peer review in an open meeting announced in the *Federal Register*. Any members of the public may attend and participate in this meeting. For all HHEs conducted by management, employee representatives are guaranteed roles in the evaluation process. Final reports based on these evaluations are sent to these representatives and to national labor representatives; they are also posted in the workplace.

Description of Risk Assessment Reports

Criteria documents provide detailed reviews and critical evaluations of all available information pertaining to an occupational hazard. Each document contains a recommended standard, presented and summarized in the first chapter. After a discussion of the purpose and scope of the document comes the body of the report, which contains a review and evaluation of all pertinent data, including indication of data gaps or inconclusive results. This segment of the document concludes with the rationale for recommended standards and compares the recommended standard with other standards currently or previously proposed. Research needs to amend disparities in available data and clarify results are noted. The final section lists references and appendices containing the recommended methods of sampling and analytic methods for hazard determination, along with other information.

Each current intelligence bulletin begins with an abstract summarizing the results of studies on the hazardous process or substance. Statements concerning proposed future research or recommended standards may also be included. The body of the document briefly discusses the physical and chemical properties of the hazardous material; its production, use, and potential for occupational exposure; current exposure standards and guides;

toxicity reported in animal studies; and known human health effects. HHEs are relied on when available for preparing a current intelligence bulletin. A reference list is included.

An HHE begins with a brief description of the problem identified in the workplace and the history and present conditions in the workplace. The materials and methods used to isolate and identify the hazard are described. The report then summarizes information drawn from other NIOSH documents, the scientific literature on adverse effects associated with the material and process. Results of medical, epidemiologic, and environmental surveys conducted at the workplace are summarized. Possible hazards are identified and characterized from toxicity data found in the literature. Based on these evaluations, recommendations are proposed for any changes in materials and procedures to ameliorate any hazardous conditions identified in that workplace.

Mechanisms for Forwarding Results for Policy Decisions

Copies of all NIOSH policy statements are formally transmitted with a letter from the institute director through the CDC director to the assistant secretary for labor and the ASH. Because HHEs, with their recommendations for reducing workplace hazards, are also submitted directly to the employer, these assessments have significant potential for improving worker health and safety.

Procedures for Disseminating Findings to the Public

Approximately 5,000 printed copies of each criteria document and current intelligence bulletin are provided to NIOSH staff and regional offices, selected universities, and individuals on the mailing list of the NIOSH publication office. Through the Government Printing Office (GPO), the National Technical Information Service (NTIS), and the Central Information System (CIS) of the WHO, documents are made available to the public. The bulletins are mailed to all individuals, organizations, or corporations on the mailing list of the NIOSH publications office, including trade and professional associations, labor organizations, and government agencies, and copies are made available to other interested groups through the publications office. In addition to the NIOSH's quarterly announcement of publications that is sent to approximately 8,000 people involved with occupational health, publications are announced in the *BNA Reporter* and other similar newsletters.

Results of informal, unwritten HETA investigations are sent in the form of a letter to those employers or employee representatives who requested the investigation. In cases in which formal reports have been prepared, copies of full HHE reports are sent to the individuals requesting the investigation and to the employer. Employers are required to post copies of the reports at or near the workplaces of affected employees for at least 30 calendar days. The employer must request that the NIOSH mail copies of the report directly to the affected employees, whose names and addresses must be furnished by the employer; in this latter case, the employer need not post the results.

Formal HHE reports are distributed within the NIOSH and the OSHA and to the public through the same mechanisms by which other NIOSH documents are disseminated. In addition, if HETA staff determine that any conditions exceed current OSHA standards, the OSHA is notified. HHE reports may also be published as articles in the *MMWR* and in technical and trade journals.

Evaluation of the Public Health Effects of Assessments

Because NIOSH recommendations are implemented through indirect means, it is difficult to evaluate the impact of NIOSH policy statements on workers. Through expert testimony and written comments, the NIOSH participates in approximately three-fourths of the OSHA regulatory efforts so that the NIOSH recommendations can be voluntarily implemented in the workplace and provided to workers. NIOSH policy statements also provide a basis for recommendations issued as a result of HHEs and made available to the employer, worker representatives, and workers.

After conducting HHEs, the NIOSH periodically conducts a follow-up telephone survey of employer and employee representatives to determine whether the evaluation report on their facility adequately addressed the occupational health problems and if the recommendations were implemented. These surveys indicate a high degree of compliance with the HHE recommendations. Occasionally employers request follow-up surveys to ascertain the effectiveness of the implemented recommendations.

The effectiveness of the HHE program in disseminating information to other affected industrial and occupational groups is more difficult to assess. However, there has been an increased dissemination of these results through trade journal articles and other publications over the past few years.

CASE STUDIES

Missouri Dioxin Assessment: CEH

When the Missouri Department of Social Services asked the CDC to help in the investigation of contaminated soil in Missouri following reports of dead animals in the spring and summer of 1971, and the illness of a child at the end of the summer of 1971, the CEH responded with a detailed investigation. Investigations from 1971 to 1974 identified the contaminant as 2,3,7,8-tetrachlorodibenzodioxin (TCDD or "dioxin"). In 1975, the CDC issued a report on the investigations and recommended action to limit exposure to materials containing dioxin and to evaluate the health of previously symptomatic individuals.

In 1979, after the EPA received an anonymous telephone warning that toxic wastes were buried in Missouri, drums of TCDD-contaminated waste were found and removed. A previously held belief that the half-life for degradation of dioxin in soil was less than a year proved to be incorrect. On returning to the original sites where illness had been reported in 1971, the EPA discovered levels ranging from 10 ppb to 300 ppb in a landfill, and as high as 1,750 ppb where the child had become ill.

In February 1982, the EPA reopened the investigation and conducted new environmental sampling. The EPA requested the CDC's assistance in determining what concentration of dioxin in soil "would not pose an unreasonable risk to human health." The CEH agreed to review new sampling data from the EPA and other literature on the toxic effects of TCDD and to recommend a level of TCDD in residential soil that would pose a "level of concern" of significant risk to human health and would be used by the EPA to determine necessary clean-up levels of residential soil.

Hazard Identification

Investigations into the toxicity of TCDD were begun in the 1950s. The EPA reports TCDD to be one of the most poisonous synthetic chemicals on a weight basis. Human exposure to TCDD induces chloracne, polyneuropathy, and liver dysfunction. In studies of laboratory animals TCDD has been shown to be teratogenic, embryotoxic, and carcinogenic.

Hazard Characterization

In the course of its assessment, the CEH reviewed all toxicological information that it considered useful for the development of a quantitative risk determination. TCDD was reported to be a teratogen in several strains of mice, and to produce fetotoxic effects in rats. Reproductive effects were species-dependent, with subhuman primates being among the most susceptible species.

Results of several cancer studies were examined. A carcinogen bioassay conducted by the NTP was positive in Osborne-Mendel rats and $B6C3F_1$ mice. Other carcinogenicity studies conducted with doses similar to those used in the NTP study also showed an increased incidence of tumors in the liver, but no correlations in other target organs were noted. The CEH attributed this latter finding to differences in methods of administration (gavage vs. food) and in the animal strains used.

For carcinomas of the liver in female rats, the smaller lower confidence bound on the "virtually safe dose," extrapolated from risks observed at high doses estimated by the linearized multistage model using an added risk of 1/1,000,000, was calculated to be 28 fg/kg body weight/day for liver and as high as 1428 fg/kg body weight/day for an increased risk of 1/1,000,000 in less sensitive tissues. The levels for an increased cancer risk of 1/100,000 are ten times higher. Details of these calculations are included in the assessment, although the CEH noted that this approach could overestimate the risk.

The CEH also reviewed studies of human health effects based on worker exposure and environmental exposure to TCDD. Specific problems affected each study, but a universal problem in these studies was the lack of any direct, objective measurement of exposure.

Exposure Characterization

It was necessary for the CEH to determine how humans might absorb TCDD from contaminated soil. Three routes of exposure were considered: (1) dermal absorption through direct contact with soil; (2) ingestion of soil; and (3) inhalation of dust containing TCDD. This assessment did not examine whether environmental TCDD could enter the food chain.

Estimates of total lifetime dose were based on a combination of various assumptions and available scientific data. Calculations of the surface areas that 1 to 10 grams of soil could cover and of the surface areas of the palm of one hand of medium-size children and adults illustrated to the CEH that it was reasonable to assume that people would make contact with 1 to 10 grams of soil.

A GI absorption rate of 30 percent was estimated from bioavailability studies. The estimates of amount of soil ingested are dependent upon activities and age. A pattern of ingestion per day dependent on age was calculated ranging from 0 to 10 grams.

The CEH assumed that levels of TCDD in contaminated airborne dust were the same as levels in outside soil. Since airborne dust levels in vegetated areas are small (micrograms/m^3 air) and exchange of air for adults ranges from 10 to 40 m^3/day depending upon activity, the CEH chose 15 m^3 of air exchanged per day for estimate calculations.

Other assumptions were that exposures would occur for only six months of the year and that contamination was uniform over a given area. The CEH recognized that the doses calculated were, in some sense, worst-case estimates.

Risk Determination

By combining the results of the hazard characterization with estimates of exposure from soil contamination, an "acceptable" concentration of 1 ppb in residential soil was derived. This determination, however, was complicated by many uncertainties that were highlighted in the CEH assessment resulting in part from (1) insufficient data on the toxicology of TCDD; (2) insufficient information about exposure of people to soil; and (3) insufficient information about intake of TCDD by humans from soil.

Calculation of the "virtually safe dose" (VSD) for TCDD was based on two independent carcinogenicity studies. The multistage model was fitted to tumor incidence at various anatomic sites, and the chi-square value for the goodness-of-fit test was calculated. For comparison, the linear model was fitted when the best-fitting multistage model was nonlinear.

A dose range for an increased cancer risk of 1/100,000 was calculated from the data in these two studies to be 280 to 14,00 fg/kg body weight/day. Corresponding figures for an increased cancer risk of 1/1,000,000 are 28 to 1,428 fg/kg body weight/day.

A direct conversion was made from rodents to humans. While no scientific evidence compels this decision, the report noted that ". . . there is also no scientifically justified alternative form of extrapolation . . . that should be preferentially used."

Aspirin and Reye Syndrome: CID

Reye syndrome is a rare, acute, life-threatening condition characterized by vomiting and lethargy that may progress to delirium, coma, and death. It occurs most commonly in children who are recovering from viral infections, particularly influenza and chickenpox, and who have received salicylates (aspirin). Approximately 600 to 1,200 cases are reported each year in the United States, most of them in persons between the ages of five and sixteen years of age, although the true incidence (especially of mild cases) is likely to be much higher. Death occurs in 20 to 30 percent of reported cases, and permanent brain damage has been reported in survivors.

In June 1982, the CDC published a surgeon general's advisory on the use of salicylates and Reye syndrome in the *MMWR*. Subsequent to the surgeon general's advisory, the FDA announced that salicylate labeling might be changed to reflect the risk of Reye syndrome. The FDA announcement prompted a call by the American Academy of Pediatrics for more conclusive evidence of the association of aspirin administration and Reye syndrome. As a result of this statement, the DHHS secretary announced that new government-supported studies were necessary to help resolve scientific disputes over the reported link between Reye syndrome and salicylate-containing drugs. A full-scale study began in mid-December 1984, but the nature and strength of the association between Reye syndrome and salicylates has not yet been fully resolved.

Hazard Identification

The Viral Diseases Division of the Bureau of Epidemiology (now known as the CID) of the CDC began to monitor the incidence of Reye syndrome in December 1973 during an anticipated influenza epidemic. Surveillance was increased in 1976, again in anticipation of an influenza epidemic. Reye snydrome has been under continual surveillance since then.

The causative mechanisms that lead to the disease are still not known, through the first suggestion that Reye syndrome is associated with the ingestion of salicylates was made in 1962, even before the initial report (1963) of the disease.

Hazard Characterization

On November 7, 1980, the *MMWR* published a review by the CID of four case-control epidemiologic studies conducted by state health departments in Arizona, Ohio, and Michigan that confirmed an association between Reye syndrome and salicylates taken during an antecedent illness. The Arizona case-control study examined medication histories of seven patients with Reye syndrome and 16 ill classmates, with interviews conducted three to four weeks after the onset of the antecedent illness (influenza AH1N1). The major finding of the study was that all seven of the cases, but only 8 of the 16 controls, gave a history of salicylate ingestion during illness.

Of the two case-control studies performed by the Michigan Health Department, the first surveyed 25 cases and 46 controls with interviews conducted an average of 45.4 days and 55.3 days, respectively, after onset of the illness. Cases and controls were retrospectively matched for fever; salicylate ingestion occurred significantly more often in cases than controls. The second Michigan study recorded daily medication use for 12 cases and 29 controls, interviewed an average of 4.8 days and 122 days, respectively, after the onset of the illness. On day 1 of the antecedent illness, a significant increase of cases had ingested salicylates in comparison to controls.

A case-control study conducted by the Ohio State Department of Health examined the possible relationship between Reye syndrome and medications taken during the antecedent illness. Salicylates, including those contained in various compounds, were the only medications taken significantly more frequently in cases than controls.

Exposure Characterization

The CDC did not directly estimate exposure to salicylates among patients at risk of developing Reye syndrome. According to exposure data among control groups in the four studies and in subsequent surveys, however, between 40 and 70 percent of children may be exposed to salicylates during viral illnesses. The lower percentages have been obtained in more recent studies and surveys.

Risk Determination

In its analysis, the CID presented the strengths and weaknesses (or uncertainties) of the four studies. The major strength was that all four compared medication histories of cases with carefully matched controls. Potential problems were:

- Differences in parental recall that could have contributed to the differences seen in aspirin usage between cases and controls;
- Cases where a more severe antecedent illness may have led to

an increased usage of medications (the more severe antecedent illness may, in this case, have increased the risk of developing Reye syndrome); and

- Differences between cases and controls that may have been related to differences in antecedent illnesses, since cases and controls had not suffered the same viral infections.

The CID addressed each of these shortcomings individually and presented evidence that such problems were unlikely to have contributed to the reported association between salicylates and Reye syndrome:

- Only aspirin or salicylate-containing compounds were found to have been taken more frequently by cases than controls, and acetaminophen-containing compounds were taken by significantly fewer cases than controls. These observations suggest that differences in parental recall did not contribute substantially to the differences reported in aspirin usage.
- Two of the studies (those done in Michigan and Ohio) specifically addressed the question of whether differing histories of elevated temperatures (a major reason for taking salicylates) could have led to differences between cases and controls in salicylate usage. In the Michigan study, cases and controls were matched for degree of fever and the difference in salicylate usage remained significant. In the Ohio study, a history of fever, headaches, and sore throats did not account for the differences seen in salicylate ingestion.
- In order to control for possible differences in the types of antecedent illnesses between cases and controls, controls were selected from the same school who had had a prodromal illness within one week of that of the cases.

A second CDC review of the relation between aspirin and Reye syndrome, published in the *MMWR* on February 12, 1982, included a new study by the Michigan Health Department. A panel of outside consultants, convened by the CDC and including representatives of the FDA and American Academy of Pediatrics Committees on Infectious Diseases and on Drugs, reviewed the data to determine the strength of the association between salicylate ingestion and Reye syndrome and prepared a report for the director of the CDC. According to the *MMWR*, "After reviewing the data from all four studies and discussing the various epidemiologic and analytic methods and results, the CDC consultants concluded that it was unlikely for the limitations of the studies either singularly or in combination, to explain totally the strength and consistency of the observed association between Reye syndrome and salicylates." The panel of consultants recommended that ". . . until the nature of the association between salicylates and Reye syndrome is clarified, the use of salicylates should be avoided, when possible, for children with varicella infections and during presumed influenza outbreaks." The consultants further recommended that antipyretic agents in general not be used in such illnesses unless the need to reduce elevated temperatures outweighs other considerations. On the basis of the agency's review and that of the panel of consultants, the CDC issued the following statement: "Until definitive information is available, CDC advises physicians and parents of the possible increased risk of Reye syndrome associated with the use of salicylates for children with chickenpox or influenza-like illness." The CDC made no attempts to quantitate the risk of Reye syndrome associated with salicylate ingestion in these assessments.

A third report and review of the four case-control studies described above was published in the June 11, 1982, issue of the *MMWR*. It consisted of a "Surgeon General's Advisory on the Use of Salicylates and Reye Syndrome" with a brief description of the scientific basis for the advisory. According to the advisory, "Because the use of salicylates such as aspirin for children with influenza and chickenpox has been associated with Reye syndrome, the surgeon general advises against the use of salicylate and salicylate-containing medications for children with these diseases." The report provided a listing of organizations and government agencies that had reviewed the data on salicylates and Reye syndrome and had reached conclusions similar to those embodied in the advisory. The list included the CDC and the panel of consultants convened by that agency, the American Academy of Pediatrics Committee on Infectious Diseases, and a panel of experts convened by the CDC, the FDA, and the NIH to reach consensus on diagnosis and treatment of Reye syndrome.

Toxic Shock Syndrome: CID

The CID first reported toxic shock syndrome (TSS) as a newly recognized disease in the May 17, 1980, publication of the *MMWR*. TSS was described as a serious illness, primarily affecting young women, characterized by the sudden onset of high fever with vomiting, diarrhea, and myalagia, followed by the onset of a sunburn-like rash, hypotension and, in severe cases, shock and death. At that time, little was known about the etiology of the disease or the risks that it posed. Studies during the following month conducted by the TSS Task Force established an association between TSS during menstruation and the use of tampons. These results were published in the *MMWR* on June 27, 1980. Epidemiologic and microbiologic studies over the following two months firmly established a role for both *Staphylococcus aureus* and tampons in the pathogenesis of TSS. The findings of a second group of studies, that the Rely tampon had a greater risk than other major tampon brands, led to a consent agreement between the FDA and Procter & Gamble, the manufacturer of the Rely tampon, to remove the product from the market.

Since 1980, the reported cases of TSS have dropped greatly, although it is unknown to what extent this decrease is an artifact of passive reporting. The illness still occurs in menstruating women who are using tampons, but also occurs in children, men, and nonmenstruating women.

Hazard Identification

By May 1980 the CDC had received reports of 55 cases of the illness identified as TSS. Of those cases, it was noted that the onset of the disease was strongly correlated with menstruation. It was also noted that *Staphylococcus aureus* was present in the majority of cases that had been cultured.

Hazard Characterization

The role of *Staphylococcus aureus* and tampons in TSS and a special risk of the Rely tampon were established by retrospective case-control studies conducted by the center and by independent studies undertaken by the states of Wisconsin, Iowa, Minnesota, Utah, and Oregon.

The first retrospective CDC study sought to determine more accurately whether the relation between menstruation, *Staphylococcus aureus*, and TSS could be confirmed and whether certain practices during menstruation, such as the use of tampons, were linked to the illness. A telephone questionnaire was administered to 52 women who met the clinical case definition of TSS and to 52 age- and sex-matched controls. In the end, no significant differences were found between the patients and controls in marital status, parity, type of contraceptive method used, frequency of sexual intercourse, frequency of sexual intercourse during menstruation, brand or absorbency of tampon or sanitary napkin, or use of deodorant tampons. It was found, however, that 52 of 52 cases who fell ill during menstruation used tampons, whereas this was true for only 44 of 52 controls. On the basis of these findings, and similar results in studies conducted by the states of Wisconsin and Utah, the CDC published a qualified statement in the *MMWR* on June 27, 1980. The summary report stated that an association had been found between the development of TSS in some women and the use of tampons, though a "causal role has not been shown."

The CDC undertook a second case-control study to answer additional questions about the specific role of *Staphylococcus aureus* and whether any single brand of tampon was more strongly associated with the risk of developing menstrual TSS. Fifty TSS patients who contracted the illness in July or August of 1980 and 150 matched controls were contacted by telephone and questioned about tampon, napkin, or minipad use; brand of tampon used; and pattern of use for the menstrual cycle in which they became ill. The findings of this study showing that a substantially greater proportion of cases than controls used Rely tampons were published in the September 19, 1980, issue of the *MMWR*.

Exposure Characterization

Early in the investigation, the CDC contacted tampon manufacturers to determine the extent of tampon usage in the United States. Marketing data provided by the companies indicated that usage was frequent (approximately 70 percent of menstruating women in the summer of 1980). Thus, the CDC had figures on tampon usage (and, hence, the number of women at risk of tampon-associated TSS) before the first case-control study established the association between tampons and TSS. When the second case-control study conducted by the CDC revealed that the Rely tampon posed a greater risk than other brands, specific marketing information was sought on the product. Consultation with the manufacturer revealed that the market share of the Rely tampon had been increasing steadily since it was introduced in 1978, a fact that corresponded to the increased incidence of TSS over the same period of time.

In the course of the epidemiologic investigations, it was found that the duration of tampon use was a factor in the occurrence of TSS. The initial study conducted by the CDC, and another carried out by the Wisconsin Division of Health, showed that among the case-control pairs who used tampons, more cases than controls used tampons continuously (day and night) while menstruating. This finding, affirmed in later studies, led the CDC to issue a statement that women who choose to use tampons could reduce their risk of TSS by using tampons intermittently (i.e., occasionally substituting napkins or minipads) during the menstrual period.

Risk Determination

Based on the two case-control studies described in the hazard characterization section above, CID scientists concluded that tampon usage increased the risk of developing TSS.

The fact that an association of the disease with a specific tampon brand was not recognized in the first study was tentatively attributed to (1) the small number of cases and single-matched controls; (2) the possibility that "best friend" controls would be likely to use the same brands; (3) important changes in the brand of tampon used over time since new products and new component materials were introduced (cases were questioned about the brand used at the time of onset of disease, which may have been many months or, in some cases, years before the study while controls were asked about their most recent menstrual periods); and (4) differences in accuracy of recall of tampon brands used by cases and controls. Thus, the Rely brand was not singled out as a greater hazard than the other tampon brands until the second case-control study. Yet while the second study suggested this possibility, uncertainties still existed. Because the preliminary results of a Minnesota study and a later study conducted by the state of Utah supported the CDC finding, the manufacturer decided to remove the Rely brand from the market.

The CDC noted that removal of Rely from the market would not eliminate the TSS problem, because some cases occurred in women using other brands of tampons and because TSS is not always associated with menstruation. The CDC observed, however, that women can "almost entirely eliminate their risk of TSS by not using tampons and that women who choose to use tampons can reduce their risk by using them intermittently during each menstrual period."

Immunization-related Assessments—
1. Swine Flu: CID

On March 24, 1976, President Ford announced that he would ask Congress to appropriate $135 million to inoculate "every man, woman and child in the United States" against a new strain of influenza that had been discovered among army recruits at Fort

Dix, New Jersey. The new strain, a member of the swine flu group, was similar to the virus that had caused the pandemic of 1918-19 and killed nearly 500,000 Americans. The following discussion focuses on the scientific evidence that the emergence of the swine flu virus presented a significant risk of an influenza pandemic and that a nationwide immunization program was needed, noting changes in methodologies and assumptions since the time of the swine flu program in 1976–77.

Hazard Identification

The scientific evidence weighed prior to the swine flu immunization program included the two areas: (1) identification of an outbreak of a new strain of an influenza-like virus, and (2) determination of antibody levels of the general population.

An outbreak of flu at Fort Dix was recognized because of an increase in hospitalizations for acute respiratory disease. After the army alerted the civilian community to a possible spread of the outbreak, throat-washing specimens were evaluated by the New Jersey Department of Health. Three isolates that could not be identified were sent to the CDC, where they were characterized as a strain of swine flu. Army laboratories could not have detected the virus as they were not equipped for these evaluations. Serologic studies showed that the outbreak at Fort Dix was caused by a swine influenza-like virus, A/New Jersey/76(Hsw1N1), and the strain most prevalent in the country, A/Victoria/75(H3N2). The swine flu virus had not been previously reported in humans, though it was linked serologically to the virus of the 1918 influenza pandemic.

Antibodies to strains of swine flu had been recognized since the mid-1930s in individuals born before the 1918 pandemic. After the initial isolation of the virus causing the Fort Dix outbreak, serologic studies were used to determine the incidence of antibody to swine flu virus in humans. The frequency of the antibody is increased in persons who come in contact with swine. Diagnostic rises in antibody titer were observed in recruits at Fort Dix, in contrast to civilian counterparts of similar ages. Seroarcheology showed some antibodies in persons over 58 years of age, indicating antigenic similarities to the strain of the 1918 virus.

Hazard Characterization

The following two issues were addressed during the hazard characterization phase of the risk assessment: (1) is the virus strain serologically similar to other virus strains? and (2) is its virulence similar to that of other virus strains?

The A/New Jersey/76(Hsw1N1) strain was related serologically to the virus that caused nearly 500,000 deaths in 1918. It was already known that influenza antigens undergo periodic "recycling." Serologic data had been interpreted by some scientists as evidence that the 1957 Asian viruses had circulated before 1900 and that the 1968 Hong Kong (H3) virus was in circulation around 1900. Although the virus had been first isolated from swine in 1930, it was not isolated from humans until 1974, shortly before the Fort Dix outbreak. It was assumed that adaptations of the virus to human infection had taken place recently.

In its review of the proposed swine flu immunization program, the ACIP of the PHS noted that, even though the virus was antigenically similar to the 1918 virus, it would not necessarily have similar virulence. However, because there was no evidence that the swine flu virus did differ from the 1918 influenza virus in virulence, the 1918 pandemic and the concept of a recycled virus could not be ignored.

Another aspect of influenza epidemiology that influenced concern about a possible swine flu pandemic was the belief by some scientists that a pandemic occurs regularly, about every 10 to 11 years. Some scientists concerned about recycling predicted that it would be swine flu. Additional data gathered since the swine flu episode show, however, that pandemics do not occur at such regular intervals.

Exposure Characterization

The answers to the following questions were analyzed to determine the possible extent of exposure: (1) Is there person-to-person transmission of the disease? (2) Is there inadequate immunity in the population? and (3) What is the nature of the initial outbreak of the disease?

Since none of the recruits had come in contact with swine and many had not left Fort Dix during the period of the outbreak, researchers concluded that the virus had spread from person to person among the recruits. It could not be determined how or when the virus became adapted for person-to-person transmission or whether the Fort Dix outbreak was the first human spread or just the first recognized.

The strain was distinctly different from the contemporary A/Victoria strain. Such an "antigenic shift" is a necessary precursor for a pandemic, though only a small proportion of such shifts result in widespread human disease. It was assumed that if this virus were linked to the virus of 1918, few Americans under 50 would have been exposed to the virus, and thus few have antibodies to it.

The outbreak at Fort Dix was extensive but short-lived. Eight cases were concluded to be positive because of increases in antibody levels in two successive blood tests, and the virus was isolated from five other cases. Hundreds of recruits were noted to have elevated antibody levels in comparison to civilian counterparts. The investigation also showed that new strains of influenza can produce a limited outbreak, which was not believed common prior to this incident.

Risk Determination

After reviewing the data on the swine flu virus, the ACIP recommended that a nationwide immunization program be considered. The findings that a swine flu pandemic might occur in the United States in 1976–77 and that an immunization program was needed were based on consideration of the criteria highlighted in the preceding sections.

Today, conclusions about the level of the outbreak and the need for an immunization program might be different because of the advent of new insights and new analytic methods—generated in part by the swine flu effort itself—to draw upon in considering a decision to undertake an immunization program. Influenza immunization field trials have yielded valuable information about antibody levels and immunologic experiences of the general population. Such data help to determine appropriate dosages of the vaccine. Fuller understanding is available of the risks of vaccination, such as the occurrence of Guillain-Barré syndrome (although present data show an association between influenza and Guillain-Barré syndrome only in 1976). Another issue is the feasibility of trying to control a pandemic.

An outgrowth of the 1976–1977 immunization program was the formation of an Interagency Working Group on Influenza with representatives from the CDC, the FDA, and the NIH to coordinate the annual review of the influenza vaccine. The FDA determines which antigens will be incorporated into the vaccine, and the ACIP determines which high-risk groups should receive the vaccine. Thus, if a new virus strain is determined to present a threat of pandemic, the overall procedure for making the decision on an immunization program would be similar to that used for the swine flu program of 1977, but a much fuller range of information would be available.

2. Pertussis: CPS

Simultaneous immunization of infants and children against diphtheria, tetanus, and pertussis (whooping cough), known as DTP immunization, has been a routine practice in the United States since the late 1940s. The vaccine has played a marked role in reducing morbidity and mortality from each of these diseases. In recent years, however, there has been concern about serious and life-threatening reactions to the pertussis component of the vaccine, especially acute encephalopathy (with or without permanent brain damage), convulsions, and death.

This concern has led to reevaluations of the risk/benefit ratio for the pertussis vaccine. The following discussion focuses on data used by the CDC's CPS to evaluate the benefits and risks of the vaccine.

Hazard Identification

Case reports that adverse reactions such as seizures, encephalopathy, and death follow the administration of vaccine with pertussis antigen provided the initial indications of risk. Accurate identification of the possible role played by the pertussis vaccine in inducing these reactions has been difficult because there are no clinically distinct and recognizable symptoms. Also, the pertussis vaccine is administered to infants at a time when central nervous system (CNS) lesions resulting from other causes manifest themselves.

Hazard Characterization

A case-control study in England of the occurrence of CNS damage and its relationship to pertussis immunization was based on an examination of all hospital admissions due to CNS disease in children between the ages of two months and three years. Clinical diagnoses included infantile spasms, convulsions, encephalopathy, and epilepsy. An increased risk of encephalopathy was associated with administration of the pertussis vaccine. The frequency was estimated to be one in every 110,000 doses of DTP for acute neurologic disease and one in every 310,000 doses of DTP for neurologic disease with residual damage one year later.

In a prospective study of children from birth to six years of age receiving a DTP immunization or DT immunization to determine the rates of both minor and more serious reaction associated with the use of DTP and DT immunizations in the United States, a total of 784 DT and 15,752 DTP immunizations were given. Minor adverse reactions to the DTP immunization included redness, swelling or pain at the injection site, drowsiness, fretfulness, vomiting, anorexia, and persistent or unusual crying. More serious reactions included convulsions or a hypotonic hyporesponsive episode ("shock-like" state).

A case-control analysis of sudden infant death syndrome (SIDS) cases was sponsored by the National Institute of Child Health and Human Development (NICHD). Analysis of 800 infants demonstrated that fewer cases of SIDS were found in infants who had received the pertussis vaccine than in the controls.

Exposure Characterization

Three general assumptions were made concerning the vaccine program: (1) 90 percent of the children would receive a complete primary series and a booster (a total of five doses); (2) there is no protective effect until the third dose is received, usually at about six months of age; and (3) the vaccine is 80 percent effective in conferring immunity.

Risk Determination

In the CPS staff assessment, the costs associated with the disease are compared to those associated with the vaccine. The data, assumptions, and methods used to estimate (1) disease incidence rates with and without a vaccine program and (2) number of complications with and without a vaccine program are presented below, although the cost estimates themselves are not included.

The risks associated with the disease ("expected" complications) that were used to derive quantitative estimates were hospitalizations, deaths, and encephalitis. The risks of the vaccine included those due to a lack of effectiveness of the vaccine (i.e., the risks of the disease in a portion of the vaccinees who would not be protected from pertussis) and those attributed to the vaccine itself. Complications from the vaccine included minor reactions, convulsion/collapse, crying, acute encephalitis, and encephalitis with residual defect. Death was not included as an adverse complication of the vaccine because a casual link between the vaccine and SIDS has not been established.

Estimates were developed for a hypothetical cohort of 1 million children followed from birth to 6 years of age. The expected disease incidence rate was calculated from reported age-specific incidence rates in England and Wales, 1976 to 1981, to be 546 cases/100,000 each year for the six years. This incidence rate occurred when mean vaccine coverage was 50 percent. CPS staff estimated the expected incidence rate with and without a vaccine program, by extrapolating from the relationship between disease incidence rate and vaccination coverage in a study of a pertussis epidemic in the United Kingdom (UK). CPS staff used actual vaccine acceptance rates and disease incidence rates to estimate that annual pertussis rate at 90 percent vaccine acceptance would be 197 cases per 100,000 population aged 1 to 4 years; at 0 percent acceptance, the incidence rate in this age group would be 2,063 cases per 100,000. To determine the total number of cases in the cohort, the authors assumed that the age distribution of cases would match that reported for England and Wales. The total number of cases of pertussis per 1 million children was estimated to be 9,728 with the vaccine program and 101,876 without the program.

Estimates of complications from the disease at various ages were based on a study of 8,092 cases reported during 1974–75 in the UK. Mortality rates were calculated for two broad age groups (birth to 6 months, 6 months to 5 years). Finally, two cases of encephalitis were reported (0.025 percent) in the UK study, and this rate was applied to the total number of cases. The authors assumed that one-third of the encephalitis cases would have residual defects requiring long-term care. The following number of cases were calculated:

	Number of Cases (per million)	
Effect	*With Program*	*Without Program*
Hospitalization	1,060	11,098
Death	12.5	130.6
Encephalitis	2.4	25.5
Residual defect	0.8	8.5

The authors estimated the risk of adverse reactions associated with the pertussis vaccine from studies done in the United States and United Kingdom. Assuming that the risk of complications was the same for every dose and for all ages, they applied the rates reported in these studies to 4.5 million doses of vaccine. The expected number of cases with vaccine complications was (1) minor reaction, 1,800,000; (2) convulsion, 2,571; (3) collapse, 2,571; (4) high-pitched unusual cry, 4,860; (5) encephalitis, 40.9; and (6) encephalitis with residual defect, 14.5. The authors converted these results into numbers of hospitalizations, assuming hospitalization rates of 0 percent for minor reactions, 12.5 percent for convulsions or collapse, and 100 percent for encephalitis. Their estimates of selected events with and without a vaccine program to the U.S. national level (3.5 million children born each year) follow:

	Number of Events (per million)	
Event	*With Program*	*Without Program*
Cases of pertussis	34,048	356,566
Hospitalizations, total	6,529	38,787
Deaths	44	457
Encephalitis	162	87
Residual defect from encephalitis, total	54	29

When the risks associated with not having a vaccine program were compared with those associated with the vaccine (not including encephalitis), the benefits of a vaccine program outweighed the risks.

A sensitivity analysis of the impact of changes in estimates or assumptions on the model used was included in the assessment. Two major assumptions were highlighted: (1) The presence of a herd immunity effect and (2) the rate of hospitalization for side effects from the vaccine. Changing assumptions led to a decrease in the ratio of overall costs without a program to those associated with a vaccine program from 5.7:1 to 1.6:1 for the former assumptions and 4.4:1 for the latter. According to the discussion presented in the assessment, the assumptions made in this analysis for vaccine complications tended to "prejudice the case against vaccination." Thus the cost ratios developed in the analysis were more likely to be underestimates rather than overestimates.

The analysis was reviewed internally by the CPS and the office of the director of the CDC, and also underwent peer review before publication. The conclusions in this staff analysis provide support for the CDC's position on the continued use of the pertussis vaccine: "Pertussis is a highly communicable disease (attack rates of over 90 percent have been reported for unimmunized household contacts). It is frequently associated with complications, severe sequelae, and a high case-fatality ratio in infants. Vaccination early in life is essential." According to CDC scientists, "The vast majority of U.S. scientists and public health officials believe that the benefits of pertussis vaccine far outweigh its risks," and the agency continues to recommend that all infants except those who have had convulsions should be immunized against pertussis.

Ethylene Dibromide: NIOSH

In 1983, public awareness that the grain and produce fumigant ethylene dibromide (EDB) might cause cancer and other adverse health effects led several regulatory agencies to consider regulation of EDB. In 1984, OSHA held hearings on a proposed rulemaking for EDB. To assist OSHA in its rulemaking, of the NIOSH developed, under contract, a quantitative cancer risk assessment for EDB.

Hazard Identification

The first human exposure of EDB was reported in 1910, and the first occupational exposure occurred in 1928. Early studies of the toxic effects of EDB in animals and humans indicated that EDB affected the skin, central nervous system, kidney, liver, and lungs. Studies in 1972 and 1973 reported EDB to be mutagenic in various species, including *Salmonella typhimurium his* G46 and TA1530 and L5178Y mouse lymphoma cells. EDB was also found to cause irreversible genetic damage.

The finding that EDB could induce genetic changes led to additional animal toxicity and epidemiology studies focusing on two toxic endpoints that are related to geno-toxicity (i.e., reproductive effects and carcinogenicity). Epidemiology studies have examined the relation of EDB exposure to sterility and cancer mortality in worker populations. One retrospective epidemiology study of male workers showed a decrease in fertility in one of four plants studied, but the decrease was not statistically significant. Although two epidemiology studies have examined worker populations for cancer mortality, neither showed statistically significant increases in cancer death rates in exposed worker populations when compared to control populations.

The effects of EDB on male reproduction have been studied in animals and humans. The animal studies, performed in rats, mice, chickens, rams, and bovine bulls, established the potential for reproductive toxicity, but the human epidemiology studies did not show an effect on reproduction. In the laboratory, chronic exposure to EDB by either inhalation, dermal skin painting, or oral intubation induces tumors at multiple sites. Statistically significant increases in carcinogenic response were noted in each study.

Hazard Characterization

In the NIOSH quantitative risk assessment, reports of four carcinogenicity assays conducted in rodents were evaluated for suitability in developing a quantitative risk determination for workers exposed to EDB. Two of the four studies were not used because the routes of exposure (skin painting and gavage) were not the most probable mode of occupational exposure. The two studies used in the risk determination were inhalation studies that showed significant increases in specific tumors, including tumors in the nasal cavity.

Estimating the risk of cancer at the doses of EDB to which workers may be exposed required the following steps: (1) selection of the dose-response data used to extrapolate risk; (2) selection of an extrapolation method; and (3) interspecies conversion of doses/risks in test animals to doses/risks in humans.

Selection of Dose-Response Data. While the two inhalation studies (NCI/NTP and NIOSH) included data on both rats and mice, risk estimates were based on the rat data alone because survival was better in the rats than in the mice. (Survival rates are important, because early mortality from toxicity reduces lifetime cancer incidence in the tumor-susceptible population.) Two sets of risk estimates were then calculated: (1) using data combined from the two studies; and (2) using data from the NCI/NTP-sponsored study for male rats.

The decision to combine results was supported by the argument that in both studies EDB appeared to act directly on the epithelium of the nasal cavity, thus reducing the possible biological significance of differences in absorption, distribution, and metabolism likely to be present between the different strains of rats used in the two studies (Sprague-Dawley and Fisher). Further support for combining the data was provided by the fact that the doses used in the two studies were interspaced so that more data points on the dose response curve were provided. However, the discussion also highlighted differences between the two studies, especially in terms of design and conduct, that may have weakened the validity of combining the data. Because of the uncertainty about combining the data, risk estimates were calculated on just one of the studies as well. In the NCI/NTP study, rats proved more sensitive than mice, and male rats appeared more sensitive than female rats.

Selection of an Extrapolation Model. Two models were used to extrapolate from the doses in the animal experiments to lower doses: (1) the linearized multistage model and (2) the gamma multihit model.

The multistage model is based on the "multistage theory" of carcinogenesis, which holds that multiple, generally sequential, changes in a single cell or single locus within a cell are required before the cell becomes cancerous. This model was used because it requires few *a priori* assumptions about the exact form for the mathematical low-dose extrapolation but uses experimental data instead to estimate the shape of the dose-response curve. Because the model is capable of fitting dose-response relations from linear to highly sublinear, when the data suggest sublinearity, it should provide a more realistic measure of the uncertainty of low-dose extrapolation than a predetermined linear curve shape or a probit line. The upper confidence limit on estimated risk also becomes essentially linear for generalized polynomial extrapolation in the low-dose range. The use of the multistage model was further supported by a recommendation of a governmentwide panel (the Interagency Regulatory Liaison Group (IRLG), in its guidelines for carcinogenic risk assessment for use by federal regulatory agencies) that "whenever quantitative risk analysis is deemed necessary, linear extrapolation should always be included among any methods used."

The NIOSH also used a version of the gamma multihit model based on the "hit theory" of carcinogenesis, that one or more discrete, irreversible events ("hits") are needed to transform a normal cell into a malignant cell. The "multihit theory" proposes that several different cells or locations within cells must be transformed to form a tumor. The model used included calculation of conservative lower confidence limits and a likelihood ratio test of linearity against nonlinearity at a 5 percent level of significance. This model thus served to check the assumption of linearity of low doses and to validate the use of upper confidence limit estimates.

Interspecies Conversion. The risk assessment document also includes a list of assumptions that were used to convert the estimates or risk per unit of dose in rats to estimates of risk in humans. The assumptions included the following:

- Humans are as susceptible to carcinogenesis by inhaled EDB as the most sensitive species.
- The most sensitive tumor site is the nasal cavity.
- All of the inhaled EDB is absorbed by rats and humans.
- Rats inhale 0.14 liters air/minute; humans inhale 30 liters air/minute when working and 7 liters air/minute when resting.

- Female Fisher rats weigh 200 grams, male Fisher rats weigh 300 grams, female Sprague-Dawley rats weigh 400 grams, male Sprague-Dawley rats weigh 500 grams, humans weigh 70 kilograms.

Exposure Characterization

Occupational exposure to EDB occurs in EDB production plants, gasoline blending operations, gas stations, fumigation operations, and other settings. The current OSHA standard is 20 ppm; NIOSH recommended a standard of 130 ppb in an earlier criteria document.

Worker risk was estimated for several concentrations of EDB in air: 0, 65 ppb, 130 ppb, 1 ppm, 10 ppm, and 20 ppm. These concentrations were selected to show effects at the current OSHA standard, the present NIOSH recommended standard, and ½ the NIOSH recommended standard (65 ppb) which was proposed for an action level. Using these concentrations and assuming a hypothetical worker exposure of 8 hrs/day, 5 days/wk, 46 wks/year for 45 years, several lifetime exposures to EDB were calculated.

Risk Determination

A range of risks associated with EDB exposure was developed using the multihit and multistage models to estimate dose-response data from the NCI/NTP study and from combined data from both studies. (These risks are tabulated in Exhibits 5–1 and 5–

Exhibit 5–1 Lifetime Human Cancer Risk from Occupational Exposure to EDB Based on NCI Inhalational Bioassay (Male Rats)

	At Rest		*Working*	
Concentration	*Gamma Multihit*	*Multistage*	*Gamma Multihit*	*Multistage*
0	0	0	0	0
65 ppb	0.054	0.020	0.14	0.081
130 ppb	0.086	0.039	0.23	0.16
1 ppm	0.33	0.26	0.71	0.73
10 ppm	0.92	0.95	0.99	1.0
20 ppm	0.99	0.99	1.0	1.0

Note: This risk extrapolation used both low and high (10 ppm and 40 ppm, respectively) rat data, even though the 40 ppm group exhibited competing toxicities of EDB. Calculations performed but not reported for the low dose group alone agreed with these risk estimates within a few percentage points.

Abbreviations: EDB = ethylene dibromide, NCI = National Cancer Institute.

Source: SRI International, 1982.

Exhibit 5–2 Lifetime Human Cancer Risk from Occupational Exposure to EDB Based on Combined NCI and Wong et al. Bioassays (Rats of Both Sexes)

	At Rest		*Working*	
Concentration	*Gamma Multihit*	*Multistage*	*Gamma Multihit*	*Multistage*
0	0.005	0.006	0.005	0.006
65 ppb	0.088	0.023	0.19	0.080
130 ppb	0.13	0.04	0.26	0.15
1 ppm	0.35	0.25	0.67	0.70
10 ppm	0.87	0.93	0.99	0.99
20 ppm	0.97	0.99	0.99	1.00

Abbreviations: EDB = ethylene dibromide, NCI = National Cancer Institute.
Source: SRI International, 1982.

2.) This quantitative determination supported the conclusion of NIOSH in 1977 that the current OSHA standard of 20 ppm is not sufficiently protective. In 1977, NIOSH recommended that occupational exposure to EDB be controlled so that concentrations of EDB not exceed 130 ppb measured during any 15 minute sampling period. That recommendation was based on extrapolation of the lowest dose shown to cause cancer in animals. As a result of this quantitative risk determination, the NIOSH revised its recommendations on EDB in comments transmitted to DOL on OSHA's proposed standard of 1983. The NIOSH recommended that the permissible exposure limit be reduced to an 8-hour TWA of 45 ppb with a 15-minute ceiling of 130 ppb.

Styrene: NIOSH

In September 1983, as a part of its ongoing program of criteria development, NIOSH issued a criteria document on styrene, *Criteria for a Recommended Standard: Occupational Exposure to Styrene*. The document included an assessment of the adverse health effects of exposure to the chemical and a recommended occupational health standard.

Hazard Identification

The major adverse effects identified in humans were CNS depression and irritation of the skin, eyes, and upper respiratory tract. Data supporting these conclusions came from studies of experimental exposure of humans and animals to styrene and case reports of workers exposed to styrene.

In addition to the effects mentioned above, the criteria document stated that styrene might cause damage to central and peripheral nervous systems, birth defects, chromosomal aberrations, sister chromatid exchanges, unscheduled DNA synthesis, impaired pulmonary function, liver injury, and cancer. Since the data on these effects came largely from limited animal and short-term studies, however, they were not considered to be sufficient to conclude that such effects would occur in workers exposed to styrene. The document stated that "further study of these latter effects will help to elucidate their etiology."

Hazard Characterization

Four studies have been conducted in rodents to determine the carcinogenicity of styrene. Three of the four studies gave "suggestive" but not "convincing" evidence of the carcinogenicity of styrene, while the fourth study was inconclusive because problems with concurrent disease in the test animals limited the reliability of the findings. Inconclusive epidemiological studies added further weight to the judgment that the data were too uncertain to determine whether styrene is a human carcinogen.

CNS effects have been observed at concentrations of about 100 ppm. Experimental and clinical studies have reported CNS effects at concentrations less than 100 ppm, but only a small number of subjects were studied in the experimental groups and the clinical studies included a wide range of concentrations. Animal studies suggest that styrene is hepatotoxic, but only at concentrations much higher than those found in the workplace. Styrene has not been found to be teratogenic, embryotoxic, or fetotoxic.

Exposure Characterization

The number of U.S. workers exposed to styrene is difficult to estimate because many facilities produce styrene and many more use styrene or styrene-containing products in production and manufacturing processes. The NIOSH estimated that at least 30,000 U.S. workers in 1,000 plants are potentially exposed to styrene on a full-time basis, and that over 300,000 U.S. workers in over 20,000 facilities are potentially exposed to compounds containing styrene, but the later group may come in direct contact with styrene only periodically or not at all. Data on styrene concentrations in different occupational settings were also presented and used to identify industry sectors most likely to have a population at risk or most likely to need controls.

Risk Determination

The NIOSH recommended that worker exposure to styrene should not exceed 50 ppm as a TWA (time-weighted average) concentration for up to a 10-hour workshift, 40-hour workweek. To prevent CNS depression and irritation of the eyes and respiratory tract, exposures should not exceed a 15-minute ceiling concentration of 100 ppm. The NIOSH also recommended investigation of other health effects and stated that the current occupational exposure limit was not sufficiently protective.

The criteria document was critically reviewed internally, then by external consultants and federal agencies. After DSDTT considered all comments from reviewers and incorporated them as appropriate, the office of the director of the NIOSH performed a final review before official NIOSH recommendations were sent to the OSHA for consideration in standard setting.

Grain Elevators and Feed Mills: NIOSH

Grain elevators and feed mills have a long history of high accident and injury rates, the best known of which are from dust explosions. In September 1981, the DSR of the NIOSH published guidelines for *Occupational Safety in Grain Elevators and Feed Mills* based on the DSR's investigations of worker safety in those settings. The guidelines were developed to promote safe work practices and engineering controls that could be used to reduce the number of accidents and injuries, and to train workers in the identification and awareness of hazards and their controls.

Hazard Identification

Workers in grain elevators and feed mills are exposed to a wide variety of conditions that could lead to accidents and injuries in the performance of their work. The grain dust explosion hazard has been know for years. Of all industrial dust explosions in the United States, those in grain elevators are the most frequent and cause the most injuries and property damage. The United States Department of Agriculture (USDA) recorded 399 explosions in grain elevators and feed mills in the United States over the 23-year period from 1958 through 1980, resulting in 679 injuries and 185 deaths. Injuries resulting from explosions are, however, only a small percentage of overall injuries. According to the Bureau of Labor Statistics (BLS), of 8,000 voluntarily reported injuries in feed mills in 1976, only 23 resulted from explosions.

The DSR estimated from BLS data that feed mill establishments have an injury incidence rate approximately 1.7 times that of total industry, and 1.2 times higher than all manufacturing industries. The National Safety Council (NSC) injury data also indicated that the frequency rate of disabling injuries for grain mills is about 1.7 times higher than industry average, and that the severity rate is about twice as high as the industry average. NSC statistics for grain elevators show the frequency rate to be only 1.5 times the industry average, but with a severity rate almost 6 times as high. The DSR noted, however, that reporting is voluntary and that these data underestimate the risks.

The single largest safety concern in grain-handling and processing facilities is that of dust fires and explosions. According to the National Fire Protection Association (NFPA), about 48 percent of all dust explosions in the United States from 1900 to 1956 occurred in industries handling grain, feed, and flour. The USDA has estimated from NFPA data that during the period from 1958 through 1975 there was an average of 2,700 fire incidents per year in the grain-handling industry. Because of inadequate reporting systems, these USDA estimates may be understated by at least a factor of 2.

Hazard Characterization

In addition to the general hazards of industrial work, employees of grain elevators and feed mills face significant additional hazards. The DSR reviewed accident reports and was able to characterize general industrial safety hazards in terms of the following conditions:

- *Facility.* Accidents may occur as a direct result of worker interface with facility walking surfaces, stairs, ladders, and manlifts. Overhead obstructions, narrow aisleways, or elevated work stations may also contribute to accidents.
- *Equipment.* Employees of grain elevators and feed mills frequently interface with moving machinery such as conveyors, drive motors, drive belts, gears, and pulleys. Associated hazards include pinch points and nip points (where two moving pieces of machinery, or one moving and one stationary piece of machinery come together), inadequate lockout systems, and inadequate cross-over points.
- *Vehicles and Lifting Equipment.* Various types of vehicles and lifting equipment are used in and around grain elevators and feed mills. Receiving and shipping areas are generally the areas of highest activity. Associated injuries usually result from

use of heavy equipment, lack of adequate training, operation outside of design limits, lack of proper equipment maintenance, and lack of employee attention.

- *Manual Handling.* Many handling operations are performed manually. Improper handling techniques and handling of oversize or overweight material results in back injuries and sprains.
- *Confined Spaces.* Employees must often work in confined spaces such as bins, tunnels, tanks, and pits, where accessibility, maneuverability, and communication with standby personnel are difficult. Working in confined spaces frequently results in death.
- *Health Hazards.* The primary heqlth hazards in grain elevators and feed mills are exposure to toxic fumigants and pesticides, and inhalation of grain dust.

A dust explosion hazard exists whenever combustible dusts accumulate or are generated as a result of grain handling or processing. The DSR characterized four conditions that must be addressed to reduce risks:

- *Airborne Dust Concentration.* Airborne dust must be present in a concentration within the explosive limits. Most reports of lower explosive limits range from 20 to 70 g/m^3; and reported upper explosive limits vary from 2,000 to 3,000 g/m^3. Peak explosive pressures generally occur near concentrations of 1,000 g/m^3. Layered dust poses a significant hazard in that it may be ignited, and if agitated may lead to explosive airborne concentrations.
- *Oxygen Concentration.* The concentration of oxygen must be sufficient to sustain rapid combustion. Oxygen concentrations greater than 12 percent are sufficient to sustain combustion; ambient air is about 20 percent oxygen.
- *Ignition Source.* An ignition of sufficient duration and energy must be present. The minimum amount of energy required to ignite common grain dusts, such as corn and wheat, ranges from 30 to 60 millijoules. Ignition may occur as the result of thermal, mechanical, or electrical energy release.
- *Confinement.* Dust explosions occur only in relatively enclosed spaces. Confinement may occur in elevator bins, grinders, dust-collection equipment, and, in many cases, the basic facility structure.

Exposure Characterization

Approximately 15,000 grain storage and handling facilities in the United States operate year-round or seasonally, with great fluctuations in the work force. The number of employees range from two to three in small country elevators to 150 or more in large export terminals. The DSR did not discuss employment patterns in feed mills; however, it is assumed that they are similar to those in grain elevators. BLS statistics show that in 1976, 135 thousand workers were employed in the grain mill products industry, and a total of 192 thousand workers were employed in the prepared feeds and farm product raw materials industries.

BLS data on occupational injury and illness rates classified by employment size show that for grain mill products the lowest incident rates are achieved by employers with over 1,000 or less than 20 personnel. For farm products, a similar trend exists, with the lowest rates achieved by the largest and smallest employers.

Risk Determination

Based on analysis of grain elevator and feed mill accident statistics and case studies, the DSR found that the rate of injury incidence in these facilities is approximately 1.5 to 1.7 times that for all industry, and that the injury severity rate is 2 to 6 times as great as the total industry average. Most injuries in grain elevators and feed mills result from general industrial safety hazards. Though explosions are only a small percentage of all accidents and injuries occurring in grain elevators and feed mills, they cause the most severe injuries and damage.

Having assessed the health risks, the DSR provided targeted risk management recommendations. The DSR determined that injury incidence rates could be reduced through the use of safer work practices, such as lowering both airborne and layered dust levels, increasing ventilation, monitoring hot work more strictly, and promoting general safe work practices through proper training and use of equipment. Although it is recognized that some grains such as rice are less susceptible to dust explosions, sufficient data were not available to correlate the recommended guidelines with the relative hazard of the commodity being handled. The DSR incorporated the above findings into a set of safety standards designed to reduce the number of accidents and injuries in existing facilities. DSR's analysis and recommendations contributed to the technical basis for OSHA rulemaking on grain elevator and feed mill safety regulations. As of January 1985, OSHA had completed hearings, but had not yet issued regulations.

Chapter 6

FOOD AND DRUG ADMINISTRATION

The programs of the Food and Drug Administration (FDA) are designed for a single purpose: consumer protection. The FDA's mission is to ensure that food is safe, pure, and wholesome; that human and animal drugs, biological products, and therapeutic devices are safe and effective; and that radiological products and procedures for the use of these products do not result in unnecessary exposure to potentially harmful radiation. In fulfilling its mission, the FDA routinely undertakes health risk assessments to determine the safety of products within its jurisdiction, which serve as a basis for regulation. All five centers of the FDA—the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Veterinary Medicine (CVM), the Center for Drugs and Biologics (CDB), the Center for Devices and Radiological Health (CDRH), and the National Center for Toxicology Research (NCTR)—are directly involved in health risk assessment activities. The chapter opens with a discussion of general procedures and policies related to the conduct of risk assessment in the five centers and concludes with case studies that highlight the analytic processes characteristic of the FDA's risk assessments.

AGENCY OVERVIEW

Food and Color Additives and Cosmetics: CFSAN

Although the provisions differ in detail, both food and color additives are subject to premarket approval and are handled in a similar fashion. They are regulated by the Center for Food Safety and Applied Nutrition (CFSAN). Medicated cosmetics such as deodorant soaps or fluoridated toothpastes are regulated as drugs by the Center for Drugs and Biologics (CDB).

Mandate

Direct and indirect food additives are regulated primarily under Sections 201(s) and 409 of the amended Food, Drug, and Cosmetic Act of 1938. Before a food additive may be used lawfully, a regulation must exist under Section 409 prescribing the conditions under which such additive may be safely used. One provision of Section 409, the Delaney clause, states that "no additive shall be deemed to be safe if it is found to induce cancer in man or animal."

Section 201(s) defines "food additive" as:

> *Any substance, the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe [generally recognized as safe-GRAS] under the conditions of its intended use; except that such term does not include—*
> *(1) . . . .*
> *(2) . . . .*
> *(3) . . . .*
> *(4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph [prior sanctioned] pursuant to this Act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. 71 and the following).*

Thus, under Section 201(s), ingredients that are either "generally recognized as safe" (GRAS) or "prior sanctioned"—both varieties of grandfather clauses—are not considered food additives. Hence, both categories are exempt from the requirements of Section 409 and technically not subject to the Delaney clause, although the act does not specify a procedure for determining whether a substance is GRAS or prior sanctioned. Both GRAS and prior-sanctioned substances are, however, subject to the general adulteration provisions of Section 402(a)(1).

Color additives are specifically excluded from the definition of food additives under Section 201(s), but Section 706 sets forth a premarket approval process for color additives. In addition, there is a specific Delaney provision for them. Unlike food additives, there are no statutorily mandated GRAS or prior-sanctioned color additives, although the CFR, parts 182 and 184, lists additives affirmed as GRAS by the FDA, and part 181 lists specific prior-sanctioned food ingredients.

The Food, Drug, and Cosmetic Act of 1938, as amended, gives the FDA the statutory authority to regulate cosmetic ingredients and formulations. Section 601 states that a cosmetic shall be deemed to be adulterated "if it bears or contains any poisonous or deleterious substance, which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or, under such conditions of use as are customary or usual. . . ."

Organizational Placement

The CFSAN is the focal point of the FDA's regulation of foods for human consumption and cosmetics. Specifically, the CFSAN is responsible for regulating food additives, color additives, food contaminants, and cosmetics. The Office of Toxicological Sciences within the CFSAN is responsible for risk assessment.

Agenda Setting

The mechanisms for determining the regulatory agenda for new additives differ from the mechanism for additives already approved.

New Additives. The process for the FDA approval of new food additives and color additives for both foods and cosmetics begins with the submission of a petition to the Division of Food and Color Additives. The FDA must act on the petition within 180 days unless the clock is stopped by FDA requests for more information. There is no mechanism for setting priorities among incoming petitions; each must be acted on within 180 days.

Approved Additives. The CFSAN has a formalized process for retrospective or cyclic review of food and color additives already approved. The methods and criteria for assigning priorities for review and further toxicological testing of approved additives are set forth in a 1982 the FDA document titled "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food." Briefly, the ranking criteria include the concern level (described below), results of previously performed toxicological tests, and the amount of information available (the less information, the higher the priority). The priority ranking procedure also allows consideration of exposure information, economic and administrative realities, and the use of expert judgment.

Cosmetics. Although the FDA monitors cosmetics for safety by investigating consumers' complaints and health professionals' reports of adverse reactions, there is no formal mechanism for setting priorities among cosmetics selected for review.

Risk Assessment Methods

The sponsor (generally the manufacturer) of the food additive being considered for approval must identify any human health hazard associated with the use of the additive. While no fixed battery of tests is required for every food additive, the sponsor must conduct appropriate toxicological testing. The FDA guidelines mentioned above outline the tests considered appropriate by the CFSAN. The process is similar for both new additives and approved additives undergoing review.

The extent and type of required toxicological testing for a food additive depend on its potential adverse effects on human health. After considering the expected uses of the additive, its probable extent of use, its chemical structure, its absorption, distribution, and metabolism, and its observed biological effects the CFSAN staff assesses the overall potential for adverse health effects and assigns to the food additive a Concern Level classification. The Concern Level classification system requires the most extensive toxicological testing for additives with large expected exposures, reactive structures (chemical structures similar to other compounds known to produce toxic effects), adverse toxicological effects at low doses, or adverse effects after short durations of exposure. Conversely, compounds with low expected exposure, unreactive structures, or few adverse effects are subject to more limited toxicological testing.

The Delaney clause requires that the FDA adopt a "no-risk" approach for carcinogenic food additives; the FDA cannot approve petitions for their use. However, if the sponsor provides evidence that a food additive is not a carcinogen, the additive is generally regulated on the basis of available toxicity data and estimated levels of human exposure. The Cancer Assessment Committee (CAC) in the OTS determines whether, on the basis of a fair evaluation of all available data, a substance under consideration is an animal or human carcinogen. Because of the "no-risk" nature of the Delaney clause, further inquiry into the human relevance of the animal data and quantiative (e.g., dose-response) assessments is not always performed. For some substances, such as contaminants, however, a consideration of the degree of risk is legally permissible, and scientists from various divisions collaborate to gather exposure characterization data.

For noncarcinogenic toxicities (e.g., organ toxicity, reproductive toxicity), the FDA uses the widely accepted toxicological concept of a threshold: a concentration, which may be different for each additive and each specific toxicity, below which there is presumed to be no effect. Several steps are used to translate this theoretical concept into practical terms. The first is experimental definition of a no-observed-effect level (NOEL)—that is, the highest dose at which specified effects are *not* demonstrated in laboratory experiments (usually with small samples) conducted in appropriate ways. A food additive sponsor must submit studies to the FDA that demonstrate NOELs for specific toxicities. On the basis of this data, the FDA then applies a safety factor of 10 to 1,000 to calculate an acceptable daily intake (ADI) (ADI = NOEL/safety factor) for humans. In most cases a hundredfold safety factor is applied, but if a human NOEL can be determined directly from toxicity data, the safety factor may be reduced to 10, whereas if only subchronic animal studies are available, a safety factor of 1,000 may be chosen to provide an adequate margin of safety.

Once an ADI for a food additive is determined, a tolerance for that substance in a particular food stuff must be established on the basis of the amount needed for the additive's functional requirements, a source of human exposure. The ADI is then compared to the estimated maximum likely exposure to determine whether the additive, used as proposed, is to be considered safe. To be approved for marketing, a substance must have a tolerance below the ADI.

The FDA's approach to determining the risks of color additives is essentially the same as that for food additives. The sponsor must provide evidence that a color additive is noncarcinogenic, conduct appropriate toxicological testing to evaluate any other health hazards, and estimate its expected use. As for food additives, regulation of noncarcinogenic color additives is based on ADIs. Carcinogenic color additives are strictly regulated under a Delaney clause provision in the 1960 Color Additives Amendments to the Food, Drug, and Cosmetic Act.

The FDA published an advance notice of proposed rulemaking in the *Federal Register* on April 2, 1982, describing a new policy for the approval of food and color additives that contain carcinogenic substances. The proposed policy (referred to as the "constituent policy") states that if a constituent has been shown to be carcinogenic, but the "complete additive" when tested is not carcinogenic, the additive may be approvable, a decision reviewed by the FDA's Quantitative Risk Assessment Committee. The level of the carcinogenic constituent must also be sufficiently low that the upper limit of risk of cancer that might be caused in humans by exposure to that amount of the constituent over a lifetime still provides reasonable certainty of no harm to humans. Several additives have been approved under this policy, including D&C Green No. 6.

Assessments of risk for cosmetics are also similar to those used by the CFSAN in assessments of food and color additives. FDA regulations for noncarcinogenic toxicities are based on the threshold concept. In all CFSAN risk assessment activities, impurities associated with the substance being examined are often evaluated. If an impurity is thought to pose a significant risk, standards may be set for allowed levels of the impurity or methods of manufacture that generate the impurity may be prohibited. CFSAN exposure assessments estimate the maximum likely exposure to a substance, considering all probable exposures from all products manufactured in compliance with the regulation. This exposure is then expressed as an individual maximum exposure averaged over a lifetime.

Scientific Review

All petitions received by the Division of Food and Color Additives are reviewed by scientists within the division. If there is no evidence of carcinogenicity, the toxicological tests meet agency standards, and the proposed use does not exceed the ADI calculated by FDA staff, the staff recommends the petition for approval and prepares a document that summarizes the analysis for review at the division level. The assessment may be referred to an ad hoc external review committee if controversies cannot be resolved internally. If final agency approval is obtained, the assessment is published in the *Federal Register* and open for public comment on all aspects of the regulation, including the scientific risk assessment.

Evidence of carcinogenicity, for either new or approved additives, is reviewed by the CFSAN's Cancer Assessment Committee (CAC), which is made up of 12 FDA scientists with training in toxicology, biostatistics, chemistry, pathology, and other relevant disciplines. In the case of controversial or difficult issues, the CAC may recommend that the CFSAN refer the assessment to an established panel such as the Board of Scientific Counselors of the National Toxicology Program (NTP) or outside panels established under the auspices of the National Academy of Sciences (NAS), the Federation of American Societies for Experimental Biology, or the Universities Associated for Research in Experimental Pathology.

Public Involvement

The approval of new food and color additives and any revision of the regulations on approved additives or cosmetics is a formal regulatory process and must be conducted in accordance with the Administrative Procedures Act, which requires that approvals of petitions for new additives be published in the *Federal Register*, with time for public comment and agency response before the approval becomes effective. For amendments to the regulations on approved additives, a proposed rule must be published prior to publication of the final rule, and the FDA may be required to hold a hearing after publication of the final rule on request by any affected party.

Congressional hearings provide another mechanism for public involvement in the FDA risk assessment process. Most hearings focus on issues other than the scientific basis of risk assessment, but the uncertainties of the science may also be discussed.

Description of Risk Assessment Reports

As discussed previously, risk assessments for new food and color additives are a part of the formal regulatory process. A risk assessment that may result in regulatory action is placed in a docket available for public inspection at FDA headquarters, often with commentary as well. Summaries of the assessment are published in the *Federal Register*. A typical risk assessment report contains a hazard characterization, an exposure characterization, and a risk determination in the form of an estimated safe dose, if any has been determined. A hazard characterization contains summaries of animal studies available for each compound, including a brief description of the study design, the results, and the FDA's analysis and interpretation of the results. If there was scientific controversy over the interpretation of an experiment, both the controversy and the process used to resolve it are included in the summary. The report also provides the rationale for the NOEL and safety factor chosen.

Mechanisms for Forwarding Results for Policy Decisions

Typically, both the scientific and regulatory aspects of petitions for new food and color additives are reviewed and any conflicts are resolved at the division level. During this review, information about the risk assessment is passed to decision makers in the CFSAN through briefing memoranda and other internal documents. After a risk assessment and regulatory decision is approved at the division level, a package consisting of an action memorandum, a draft *Federal Register* notice, and background materials is prepared and forwarded through internal review processes to the CFSAN director for approval. The package is then transmitted for final disposition to the associate commissioner for regulatory affairs, to whom the FDA commissioner has delegated formal approval authority.

Procedures for Disseminating Findings to the Public

All results of risk assessments that will result in regulatory action are published in the *Federal Register*.

Evaluation of Public Health Effects of Assessments

The FDA does not directly evaluate the effects of risk assessments and regulatory actions on the public but it does monitor compliance with regulated levels for food and color additives, as well as compliance with regulations that require the removal of certain products and ingredients approved for the market. For regulated products and ingredients approved for the market, the CFSAN professional staff continues to monitor the relevant published literature and private communications from consumer and health care professionals.

Food Contaminants and Natural Toxicants: CFSAN

According to the amended Food, Drug, and Cosmetic Act of 1938 (Section 406), the law governing the regulation of food contaminants and natural toxicants is in sharp contrast to the law regulating food or color additives. The secretary has interpreted Section 406 as permitting consideration of the food's nutritional value as well as the contaminant's toxicity and the extent to which its occurrence can be controlled, and may promulgate regulations setting forth tolerances for such substances when such substances are required or cannot be avoided by good manufacturing practice. In setting a tolerance level for a toxic food contaminant, the CFSAN considers (1) an assessment of the risk posed by the contaminant; (2) an evaluation of the methods of chemical analysis available to monitor the contaminant; and (3) the effects of alternative tolerance limits on the supply of the contaminated food.

Mandate

Naturally occurring food constituents are regulated under Section 402(a)(1). Under this provision, a food is deemed to be adulterated:

> *If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health.*

The "ordinarily injurious to health" standard was interpreted by the court in *United States* v. *1,232 Cases of American Beauty Brand Oysters*, 43 F. Supp. 749 (W.D. Mo. 1942), as requiring the agency to show that the food containing the substance would be dangerous in ordinary use. This standard differs from the one for added substances ("may render injurious") and makes it much more difficult for the FDA to take action against naturally occurring substances than added ones, even if the potential risk to human health associated with a naturally occurring substance is higher. Environmental contaminants of food (e.g., PCBs in fish and milk, aflatoxin in peanuts, mercury in swordfish) are regulated under Section 402(a) and 406, "Tolerances for Poisonous Ingredients for Food."

The plain language of this section seems to envision a process whereby tolerances would be set for substances "required in the production" of food or that "cannot be avoided by good manufacturing practice." However, this section has been used primarily for the somewhat different purpose of regulating "unavoidable" environmental contaminants through the setting of administrative action levels. A recent court decision has now cast this use of Section 402(a)(1) in doubt and appears to favor the use of Section 406(c). Because Section 406 does not contain a specific Delaney-like anticancer provision and the language of Section 402(a)(1) exempts food-containing substances that do not exceed an established tolerance, there may be, as a matter of strict statutory construction, no legal bar to setting a tolerance for an unavoidable carcinogenic environmental contaminant.

Organizational Placement

The organizational placement of the CFSAN is presented in the first section of this chapter.

Agenda Setting

The FDA has no formal process for selecting inadvertent contaminants for risk assessment and possible regulation, or for establishing a priority system for the inadvertent contaminants that are selected but relies on subjective judgments about exposure as well as knowledge about toxic properties and potential hazards.

Risk Assessment Methods

FDA chemists and toxicologists cooperate with the agency field force to monitor food products and identify hazardous, unavoidable contaminants or natural toxicants. Groups of chemicals monitored include pesticides (e.g., DDT, DDE, dieldrin), industrial chemicals (e.g., PCB, PBB), metals (e.g., lead, mercury, arsenic), and mycotoxins or natural poisons (e.g., aflatoxins in peanuts). The FDA also works closely with the Environmental Protection Agency (EPA) and U.S. Department of Agriculture (USDA) to identify and determine the human health hazard of food contaminants and natural toxicants.

After a potentially hazardous food contaminant is identified, toxicological data from sources that include the open scientific literature, monographs, reports, manufacturers' data, and agency-generated data are reviewed. If the contaminant or natural toxicant is not carcinogenic, an ADI (acceptable daily intake) is defined. If the contaminant is carcinogenic, the OTS applies techniques that it deems "conservative" to estimate the quantity of the contaminant that would entail an "insignificant" risk. This risk level has not been established at a fixed level by agency policy, but a level of one in a million over a lifetime has been used as a benchmark in specific cases.

The FDA's Quantitative Risk Assessment Committee oversees these issues and generally determines the risks at the various tolerance levels by a linear extrapolation procedure. (The agency uses either a linear proportional model or some version of a linearized multistage model; the most appropriate model will be chosen depending on the physical, chemical, and toxicological properties of the compound.) The policy of the CFSAN is to use the simplest procedure that makes maximum use of toxicological knowledge and the data in hand, incorporates scientific developments in the risk assessment area, and carefully describes the assumptions and limitations of the assessment.

Tolerance levels for inadvertent contaminants or natural toxicants are based on CFSAN appraisals of their public health hazards, the economic costs of achieving tolerances, and the technological feasibility of monitoring various tolerance levels. Unlike risk assessments for food and color additives, risk assessments for contaminants and natural toxicants are used in a context (risk management) that explicitly considers the consequences of the tolerance level on the quantity and price of the food supply.

Scientific Review

The mechanism for scientific review is similar to that described for food and color additives. Although outside panels may be used to resolve specific controversies, the review is conducted primarily by FDA scientists.

Public Involvement

As with food and color additives, risk assessments for inadvertent contaminants are part of the regulatory process. Notices are published in the *Federal Register* and risk assessments are available for public review and comment.

Description of Risk Assessment Reports

A typical report deals with each major element of a risk assessment. The exposure characterization lists the foods identified as containing the contaminant and the range of contaminant levels measured. The average use of these foods (by geographical region, if necessary and appropriate) is estimated and used to determine a maximum average daily intake of the contaminant. A typical hazard characterization summarizes toxicological and epidemiological data that pertain to the contaminant in question. Finally, the risk determination section provides comparisons of estimated daily intakes and the ADI at several tolerance levels, discussing each one in terms of its impact on human health and the economic changes it would provoke. The risk assessment report also recommends a tolerance level.

Mechanisms for Forwarding Results for Policy Decisions

The mechanisms for forwarding risk assessment results for policy decisions are the same as those described for food and color additives. For contaminants, the action memorandum sets forth the economic impact of the proposed tolerance and of alternative tolerances.

Procedures for Disseminating Findings to the Public

Full risk assessments are usually not published, but a summary, including recommended tolerances, is published in the *Federal Register* as a part of the rulemaking proceedings. Full risk assessments are available for public inspection at FDA headquarters in the public docket associated with the rulemaking proceedings.

Evaluation of Public Health Effects of Assessments

If a risk assessment of a food contaminant or natural toxicant results in the establishment of a tolerance level, actual levels are monitored for compliance with the regulation. The USDA monitors pesticide residues in meat and poultry on behalf of the FDA, and notifies the FDA of violations of tolerance levels. The FDA monitors some contaminant levels through its own field surveys and through the National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics (NCHS). The CFSAN scientific staff monitors the scientific literature on new toxicological data related to food contaminants and natural toxicants, as it does for food and color additives.

Animal Drug Residues: CVM

Animal drug residues are subject to Section 512 of the amended Food, Drug, and Cosmetic Act of 1938, while ingredients of feed for animals, as food additives, are subject to Section 409. However, unlike other direct and indirect additives subject to the seemingly absolute language of the Delaney clause, an exemption is made for animal drugs or food additives administered to animals raised for food production if the animal is not harmed and no residue of the additive can be found in meat using a method of analysis approved by the secretary. Most of the following discussion refers only to animal drugs, since from the standpoint of food safety, food additives and drugs are handled in much the same way.

Mandate

Section 512 of the amended Food, Drug, and Cosmetic Act of 1938 gives the FDA the statutory authority, exercised through FDA's Center for Veterinary Medicine (CVM), to regulate drugs given to animals used for food, including meat, fish, milk, and eggs. The drug must be safe and effective when used under the conditions prescribed. Under Section 512(d)(1)F of the amended Food, Drug, and Cosmetic Act of 1938, tolerances for drug residues may be set that limit the use of the drug in food-producing animals.

In the case of direct and indirect additives for human food subject to Section 409, the addition of a human or animal carcinogen would trigger the applicability of the Delaney clause. However, in the case of animal drugs and feed additives, a modified Delaney clause applies:

> *This provisio [the Delaney clause] shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the Secretary finds (i) that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (ii) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (f) and (g)) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal . . . . (21 U.S.C. 348(c)(3)(A))*

A similar provision for animal drugs at 21 USC 360(d)(1)(H) is known as the DES exception, because it was enacted in 1962 to allow the continued use of DES as a feed additive.

Organizational Placement

In 1982, the FDA transferred responsibility for the human food safety aspects of animal drug and feed additive approval from the Bureau of Foods (now the CFSAN) to the Bureau of Veterinary Medicine (now the CVM). The CVM is responsible for evaluating the safety and effectiveness of animal drugs and feed additives and for setting tolerance levels for residues in food-producing animals. Professional staff with responsibility for assessing the risk to humans from animal drug and feed additive residues make up the Office of New Animal Drug Evaluation.

Agenda Setting

New Animal Drug Applications. The process for FDA approval of a new animal drug begins with the submission of a New Animal Drug Application (NADA) to the CVM. Once the NADA is received, the CVM has 180 days to respond. Applications are processed in their order of receipt.

Approved Animal Drugs. Although the CVM drafted a proposal to begin a cyclical re-review of animal drugs already approved, it was abandoned in 1981 for lack of resources. The CVM now has a "for cause" policy for re-review of approved drugs. A review is triggered by new data derived from several sources, including the open literature and data submitted in support of a NADA for a new use of an approved drug. There is no formal procedure for establishing priorities among approved animal drugs that require review, although drugs suspected of being carcinogens go to the top of the informal list.

Risk Assessment Methods

The sponsor of a proposed animal drug is responsible for identifying any human health hazards associated with the consumption of drugs or drug metabolites residues in the edible tissues or products of treated animals. Requirements for preapproval toxicological testing of animal drugs are similar to those for food additives. For animal drugs found to be noncarcinogenic by that testing, the FDA determines an ADI by dividing the NOEL in animals by a safety factor of 100 or 1,000. The safety factor chosen is based on the nature and extent of toxicological evidence that is available and (as for food additives) decreases with increasing toxicological data. For example, if only subchronic (90-day) animal-feeding studies are available, a safety factor of 1,000 may be considered necessary to provide an adequate margin of human safety.

Regulatory procedures are different for animal drugs found to be carcinogenic by adequate toxicological testing. In March of 1979, the FDA published a proposed rule for evaluating potentially carcinogenic animal drugs that put forth specific testing requirements and evaluation criteria in considerable detail. The "sensitivity of the method" (SOM) proposal gave an operational definition of the no-residue requirement and provided that the analytic method be chosen so that its limit of detection for residues be obtained from a risk assessment using appropriate animal tumor data, rather than a maximum feasible sensitivity. In the proposal, the FDA suggested that an insignificant level of risk of cancer was 1 in 1 million over a lifetime and that the FDA should use a linear model for extrapolating from data obtained from animal experiments to determine the permitted human exposure from the edible products of animals treated with a carcinogenic animal drug.

In response to comments received on the 1979 SOM proposal, the FDA drafted a substantially modified regulation, now known as the Human Food Safety Policy for Animal Drugs, which continues to specify the risk extrapolation procedures to be used. The present draft retains the definition of an "insignificant level of risk" of cancer to be 1 in 1 million over a lifetime as the operational definition of "no residue." The detailed testing requirements specified in the 1979 proposal have been incorporated into a set of six guidelines. FDA regulations provide that sponsors may follow the testing procedures described in the guidelines or may present alternative approaches that are equally protective of public health.

Because the 1979 SOM proposal was modified so substantially, the regulation is scheduled to be reproposed. As of December 1984, it was undergoing final review in the Office of the Secretary of the Department of Health and Human Services (DHHS).

Scientific Review

The scientific assessment of a routine NADA where there is no evidence of carcinogenicity is made within the Division of Drug and Environmental Toxicology. If there is evidence of carcinogenicity, the data are reviewed by the CVM's Cancer Assessment Committee, which works closely with the CFSAN's Cancer Assessment Committee.

If a NADA is defined, the sponsor of the new drug may ask for a review, which may take the form of an appeal to the FDA (in which case the deputy director of the CVM appoints a committee of the FDA and perhaps outside scientists), a request for a peer review by an outside group of experts, or a full evidentiary hearing before an administrative law judge.

Risk assessments of approved animal drugs that are undergoing reexamination are often reviewed by scientists outside of the FDA. Scientists from academia and such governmental agencies as the National Institutes of Health (NIH) and the NCTR have participated in recent reviews.

Public Involvement

Because the approval of a NADA is equivalent to the issuance of a new regulation, it is published in the *Federal Register*. The scientific evidence that forms the basis for approval of the NADA is available to the public in the form of a Freedom of Information Act (FOI) summary prepared by the drug's sponsor and reviewed by CVM staff.

Description of Risk Assessment Reports

Each FOI summary contains sections pertaining to the effectiveness and safety of the drug in the target animal species. If the animals or animal products are to be used as food for human consumption, a section on human safety is also included.

FOI summaries do not contain all of the data used in the assessment of safety and effectiveness. Rather, the effectiveness and animal safety sections contain summaries of the methods and results of the pivotal studies and the CVM's interpretation of these studies. The human safety section includes tolerance levels for the residues of the drug and the rationale used by the CVM to arrive at these tolerance levels, as well as summaries of animal metabolism studies that identify the metabolites of the drug and the organ(s) in which they may become concentrated. It also contains a description of the analytical methodology to be used by the USDA to monitor the residue levels in animal products. Finally, the human safety section specifies the withdrawal time—that is, the minimum time required by the regulation from the last administration of the drug to the animal until the animal is slaughtered or its products are otherwise obtained for use as human food.

Mechanisms for Forwarding Results for Policy Decisions

In the CVM, as in other FDA Centers, each risk assessment is embedded in a regulatory decision about whether to permit a substance to be marketed, and if so, for what purpose and under what conditions. The CVM center director has delegated authority from the commissioner of the FDA to approve NADAs. The center director receives the results of the risk assessment and regulatory options in a decision package that contains background documents, a briefing memorandum that highlights the important and controversial issues, a draft of the *Federal Register* notice, and a copy of the FOI summary.

Procedures for Disseminating Findings to the Public

All regulatory actions are published in the *Federal Register*. The *Federal Register* notice does not include the risk assessment for a NADA, but it alerts interested parties to the existence of the FOI summary (discussed above), which contains the risk assessment on which the regulation is based.

Evaluation of Public Health Effects of Assessments

The FDA does not directly monitor the public health effects of regulatory actions undertaken as a result of risk assessment of animal drugs. As indicated above, the USDA monitors drug and feed additive residues in samples of animal and poultry products such as meat and eggs. If the residues reported by USDA exceed the tolerance levels set by the FDA on the basis of its risk assessment, the USDA and the FDA have a range of enforcement mechanisms at its disposal.

The CVM continues to receive safety and effectiveness data once a new animal drug is approved. According to law, the drug sponsor must submit new toxicological information to the FDA as it becomes available. The sponsor must also submit drug experience reports on an annual basis, and the CVM obtains information from consumer groups, trade associations, industry, and its own contractual and in-house research. In addition, CVM scientists monitor the open scientific literature and exchange information with their counterparts in other FDA centers and government agencies. If new toxicological data suggest a major risk has been overlooked, the approved drug is subject to re-review.

Drugs and Biologics: CDB

The FDA's risk assessments of drugs and biologics are developed in the Center for Drugs and Biologics (CDB). Biologics are products having a biological origin, including blood, blood products, and vaccines used in the prevention, treatment, or cure of diseases or injuries of humans. Drugs and biologics for human use are of particular concern in risk assessment because of their importance and widespread use and because both their efficacy (benefit) and their safety (risk) must be considered.

Mandate

The Food, Drug, and Cosmetic Act of 1938 as amended provides the basic statutory authority for FDA efforts to assess and deal with the risks associated with the use of human drugs. Section 201(g)(1) defines the term "drug," and Section 505 provides authority for regulation of investigational drugs and for the approval of drugs shown to be safe and effective. Biologics are regulated under the authority of Section 35 of Public Health Service Act (42 USC 262) as well as certain authorities provided by the Food, Drug, and Cosmetic Act.

Organizational Placement

Within the FDA, the CDB has responsibility for the regulation of drugs and biologics. Most of the professional staff involved in assessing the risks of new drugs and biologics are located in one of three CDB components: the Office of Drug Research and Review (ODRR), the Office of Biologics Research and Review (OBRR), or the Office of Drug Standards (ODS).

Agenda Setting

New Drugs and Biologics. The process for FDA assessment of new drugs and biologics (both prescription and nonprescription), or of new uses for previously approved drugs and biologics, normally begins with the submission of an Investigative New Drug (IND) application. A later step in the approval process requires the submission of a New Drug Application (NDA).

The IND is used to obtain permission to ship and use drug and biological materials that are not covered by an approved NDA for qualified research investigations. The FDA must complete enough of its review of newly submitted INDs within 30 days to decide whether the proposed investigations do or do not pose an undue risk to the subjects. During this time the FDA can halt the proposed investigation. The majority of INDs are received from individual physicians who wish to use an unapproved drug on a small number of patients or to study the use of approved drugs for new therapeutic indications. In 1983, approximately 2,000 INDs were received by the ODRR.

The NDA is a request for approval to market a new drug product. Although the FDA has 180 days to complete its evaluation of an NDA, it rarely meets the deadline because of its heavy workload and the complexity of the medical and scientific issues that are confronted. Priorities for NDAs beyond "first in, first out" are based on judgments by the ODRR or the OBRR of the newness of their chemical structure and their potential therapeutic importance. A drug with a new chemical structure and potentially large therapeutic importance will be placed on a "fast track" priority through the NDA process.

Approved Drugs. In the early 1970s, the FDA undertook an evaluation of the safety and effectiveness of all ingredients then used in over-the-counter (OTC) drug products. The procedural regulations for reviewing OTC drugs are specified in 21 CFR 330.10.

The CDB monitors clinical experience in the use of approved prescription drugs through a number of programs described below. While some routine monitoring of the experience in use of products occurs, most is in response to receipt of "triggering" event data such as new toxicological data, outside petitions that request review, regulatory actions in other countries, and congressional interest. Informal mechanisms establish the priority of drugs for this review.

Risk Assessment Methods

This section details only the risk assessment process for new drugs since the process for biologics is similar. As a basic principle, the sponsor of a new drug or biologic is responsible for identifying and characterizing actual and potential health hazards associated with the use of the product.

Drugs that are already approved may also be reviewed by FDA staff in light of new data, and the approval status changed. The types of studies considered and the judgments made during this review process are similar to those used in assessments of drugs.

In the case of a new drug, the FDA's evaluation begins with the initial submission of an IND application by the drug sponsor (either individual physicians or drug manufacturers) and continues as additional information is submitted, usually over a period of several years. An initial IND submission includes chemical, manufacturing, and control information; pharmacologic and toxicologic information from animals and in vitro systems; a plan of clinical study, including information about the investigator and the facilities for the study; and certain commitments regarding appropriate research practices in new drug investigations. The focus of the initial IND risk assessment is to assure adequate safety for human subjects in the further investigation of drug effects.

Preclinical Testing. The FDA "Guidelines for Preclinical Toxicity Testing of Investigational Drugs for Human Use" were issued in 1966 and reissued in 1973. Although this FDA guideline has not been updated since that time, the Pharmaceutical Manufacturers Association's (PMA) published "Guidelines for the Assessment of Drugs and Medical Device Safety in Animals" in 1977 for use by its member companies. This PMA document reflects the consensus of a joint FDA-PMA workshop in the early 1970s and provides general guidance for using animals in the toxicity testing of new drugs in animals. The CDB is in the process of updating and expanding its own guidelines for new drug testing.

The preclinical data in the initial IND submission for a new commercial drug entity usually include pharmacology, acute toxicity, and subchronic toxicity studies in rodents and nonrodents, as well as some mutagenicity data and preliminary drug metabolism and pharmacokinetic studies in animals. Dosing in toxicity studies is by the route intended for clinical use. The period of drug administration in subchronic studies ranges from two to thirteen weeks, depending on the proposed duration of human dosing. The purpose of the preclinical studies is to characterize the drug's toxicity and its dose relationships and to identify the dose below which no prohibitive toxicity occurs.

Teratology and reproductive performance studies in animals must be submitted before a new drug is studied in women of childbearing potential. For drugs intended to be used chronically or repeatedly, animal studies of chronic toxicity and carcinogenicity studies are usually begun as soon as the early clinical studies suggest therapeutic promise sufficient to warrant further development of the drug for marketing. Thus, FDA evaluation of the pharmacology and toxicology data for new drugs, first in the IND and later the NDA, is an ongoing process to assure that appropriate, adequate, and timely preclinical information is developed to support clinical decisions about proposed or ongoing human studies as well as eventual approval for marketing.

Clinical Testing. The types and extent of clinical testing of a new drug are crucial to producing substantial evidence of safety and effectiveness needed to permit evaluation of a request to market a drug. This evidence is obtained in three phases:

- *Phase I* studies involve a small number of subjects (normal volunteers and/or patients) and are conducted under carefully controlled circumstances by clinical pharmacologists to determine pharmacologic effects, toxicity, metabolism, absorption, elimination, and safe dosage ranges. At the end of Phase I the sponsor should have preliminary information on the drug's pharmacological effects in humans, and sufficient information on the short-term toxicity of the drug and its pharmacokinetics in humans to design Phase II trials.

- *Phase II* studies are well-controlled studies conducted on a limited number of patients to determine the drug's effectiveness for treatment, prevention, or diagnosis of a specific disease and to obtain additional data on short-term toxicity. Additional toxicological studies performed concurrently on animals may be necessary to provide further support of safety. For example, reproduction studies are carried out for drugs to be used in women of childbearing potential. At the end of Phase II the sponsor should have sufficient information to determine whether the drug should be developed to the NDA stage. For an important new drug an End-of-Phase II Conference is held between the FDA and the sponsor to discuss the results to date and to identify needs for further studies.
- *Phase III* studies, involving more extensive trials, are undertaken if the information obtained in the preceding phases demonstrates reasonable assurance of effectiveness for the intended use and if the drug has potential benefits outweighing the potential risks discovered up to that point. These studies are intended to assess the drug's safety on the basis of exposure to a reasonably large population group, to appraise effectiveness for the intended use in broader patient populations than those studied in Phase II, and to obtain the additional information needed to write a comprehensive package insert, including adequate directions for use. Phase III studies may include both controlled and open studies and may more closely approximate the use of the drug in medical practice than do Phase II studies. The NDA is prepared following completion of the bulk of the Phase III studies.

Currently, the FDA has published clinical guidelines for adult and pediatric drug testing in general and for specific considerations applicable to investigation of 28 different therapeutic categories of drugs (e.g., general anesthetics, radiopharmaceuticals, and hypnotic drugs). These guidelines are intended to provide the drug sponsor with broad study design guidelines for such matters as subjects and settings, qualifications of investigators, and procedures.

Whenever possible, the same FDA staff follows a drug through both the IND and NDA processes. In addition to data developed under the IND as well as data from other sources, such as foreign trials or marketing experience reports, NDAs include (1) full reports of investigations to show that the drug is safe and effective; (2) full reports of animal studies, including those that characterize the chronic toxicity and carcinogenic potential of drugs likely to be used chronically or repeatedly once marketed; (3) a complete list of drug components; (4) a complete statement of the composition of the drug; (5) a full description of the methods, facilities, and controls used for manufacture, processing, and packaging the drug; (6) samples of the drug, various components of the drug, and laboratory standards that may be required for subsequent FDA monitoring activities; and (7) specimens of proposed labels.

The potential risks of presumably inactive ingredients (excipients) in the drug formulation are also addressed during the IND-NDA review process. If a new or unusual excipient, or an unusually large amount of a recognized excipient, will be administered, CDB staff members review published literature, CFSAN files (if the drug is also regulated as a food additive), and/or the FDA Drug Master File (a separate cross-referenced document).

The FDA uses the risk-benefit principle to make risk management decisions about whether a drug will be approved for marketing. A drug is approved only if the benefits are judged to exceed the risks (real and potential) under intended conditions of use. For drugs, vaccines, medical devices, and diagnostic aids, the term "safety" is never treated as an absolute but is thought of as inherently involving a weighing of benefit and risk. After an evaluation of the effectiveness of a product and an assessment of its identifiable risks, the benefits are weighed against the risks. A drug that has a significant effect on a fatal disease with no alternative therapy could be regarded as adequately safe despite major, even life-threatening, side effects. If there were a satisfactory alternative with less toxicity but equal effectiveness, the more toxic agent might be considered safe only for a subset of patients who do not tolerate or do not respond to the less toxic drug. When the benefit of the drug is less important, such as the relief of minor symptoms, the measure of acceptable toxicity is decreased.

Use of Advisory Committees to Perform Risk Assessments. The new drug approval process of the FDA uses 20 separate prescription drug advisory committees corresponding to the therapeutic drug groups within the six divisions of the ODRR and OBRR of the CDB. These advisory committees weigh available evidence on prescription drugs and provide scientific and medical advice to the FDA staff as a basis for decision making on new drug approvals and other regulatory actions. Staff support for each committee is provided by ODRR or OBRR as well as a committee support group within the office of the CDB Director.

Committees evaluate pertinent evidence contained in INDs and NDAs and in the literature and answer specific questions posed by the CDB staff. Among other things, committees assess the adequacy of the data offered in support of a drug's safety and effectiveness by determining whether the clinical trials of the drug were well controlled and properly conducted. In some cases, committees are asked to review IND protocols prior to the actual investigation. Committees comment on whether the benefits of a new drug outweigh the risks under the conditions in the proposed labeling, and they sometimes help on special projects such as clinical guidelines. When problems arise with prescription drugs already on the market, committees may be asked to assist FDA staff in evaluating these problems and in any benefit/risk reappraisal.

Scientific Review

Several mechanisms exist for scientific review of assessments, among them, one or more levels of supervisory review, confidential INDs and NDAs that can be reviewed by drug advisory committees, and outside consultants with special expertise hired by the FDA to assess an IND or NDA. Approval of an NDA is publicly disclosed and in the case of approval of a new antibiotic drug a regulation is published in the *Federal Register* that describes the standards and labeling that were approved. The CDB prepares a "Summary Basis for Approval" for all NDA approvals, which is available through the National Technical Information Service, U.S. Department of Commerce. The medical review is available for public review under an FOI request. A summary of the pharmacological and chemical data may also be available, though some of this information is not released because it is considered proprietary.

Public Involvement

There is no mechanism for public input into the IND process; all IND submissions are proprietary. The mechanisms for public involvement in the NDA process were described in the preceding sections.

Several mechanisms are available for public input into decisions about the review of approved drugs. Petitions for review may be filed by any individual or group, and these petitions require a formal FDA response. Congressional hearings may focus FDA attention on a particular drug or group of drugs, or on a problem use of a drug. Once a drug is chosen for review, there are additional opportunities for public input into the review process. Because a review may result in a change in the approved labeling (i.e., use) or the cancellation of approval of a drug, it is a regulatory action and must conform to the Administrative Procedures Act. Thus, the public has the opportunity to respond to notices in the *Federal Register* and to request and/or participate in administrative hearings. The FDA may hold public meetings separate from administrative hearings on particularly controversial drugs, as it did in the case of Bendectin.

Description of Risk Assessment Reports

As noted above, the CBD prepares a *Summary Basis for Approval* for each NDA it approves. These documents summarize the scientific evidence on which the favorable benefit-risk assessment was based, the FDA's final determination, and the resultant regulations for labeling and use.

Each *Summary Basis for Approval* is identified by its NDA number and sponsor, drug trade name, and drug generic name. The document contains sections describing an approved drug's indications for use, dosage form, route of administration and recommended dosage; the FDA's appraisal of the manufacturing facilities and analytical methods for its detection; summaries of animal pharmacological and toxicological data; results of human studies; and photocopies of approved labeling.

The summaries of animal and human studies describe the protocols, results, FDA interpretation of the results, and the Drug Advisory Committee's recommendations (where such a review occurred) regarding safety, effectiveness, and appropriate indications for use. The approved labeling contains sections in keeping with a required format on indications and contraindications, usage, warnings, precautions, and adverse reactions. The labeling represents FDA's final judgment on the hazards, risks, and benefits of the approved drug.

Mechanisms for Forwarding Results for Policy Decisions

Although the decision about whether to permit the clinical studies proposed in an IND is usually made by the medical group leader or division director, the final decision about approving or disapproving an NDA is made in accord with published delegations of authority. Efficacy and risk assessment results and a summary memorandum are forwarded through these administrative channels as part of the documentation supporting approval and nonapproval.

Procedures for Disseminating the Findings to the Public

The results of the benefit-risk assessment of an IND are communicated to the sponsor of the IND by letter and are not publicly available, but the approval of an NDA constitutes a publicly significant action and is communicated extensively. A substantive description of the benefit-risk assessment is available to the public in the form of a "Summary Basis for Approval."

The results of the benefit-risk assessment for an approved prescription drug are conveyed to health professionals and patients by several means. Drug labeling is approved by the FDA and must contain information such as indications for use, contraindications, adverse effects, and recommended dosage. By monitoring advertising for prescription drugs, the FDA ensures that a balanced representation of risks and benefits is presented. The FDA also requires that FDA-approved patient-package inserts accompany certain prescription products to inform patients directly about safe and effective use of the drug. Finally, the *FDA Drug Bulletin*, a newsleteer on importnat drug subjects, is distributed several times each year to health professionals throughout the country.

Reviews of classes of over-the-counter drugs are published as monographs in the *Federal Register*, which define standards for the class of over-the-counter drugs considered. They specify safe and effective ingredients and the specific symptoms for which they may be promoted, as well as rules for labeling. Notices on the production of monographs are published in the *Federal Register* in the various stages of development: Advance Notice of Proposed Rulemaking, Proposed Rulemaking, and Final Rulemaking. Public participation in the processes is invited.

Evaluation of Public Health Effects of Assessments

The CDB has several mechanisms to evaluate the safety of drugs approved in the NDA process. Both drug sponsors and the FDA monitor the use of marketed drugs to detect adverse effects that may not have been discovered or quantified during the preapproval process. Drug manufacturers are required to submit periodic reports to the FDA on adverse reactions of which they become aware, and to report any significant adverse reactions. In addition, the FDA's Drug Experience Reporting System receives reports directly from physicians and other health professionals, while the FDA District Offices' Consumer Complaint System receives information from consumers. The FDA also uses a variety of special systems of postmarketing surveillance and receives information from foreign drug regulatory agencies, including product quality as determined by chemical analysis of the product by FDA laboratories.

Less formal procedures are also used to track the safety of approved drugs. As in other FDA centers, CDB professional staff monitor the world literature on drugs, talk with their colleagues responsible for similar drugs, and follow the regulatory actions of other countries and the World Health Organization (WHO).

Medical Devices: CDRH

As with drugs, new devices for human medical care are approved for commercial distribution only on the basis of a demonstration by the sponsor that any risk is outweighed by the device's benefits when it is used as intended and recommended by the manufacturer. The administering agency is the FDA's Center for Devices and Radiological Health (CDRH).

Mandate

The regulation of medical devices is authorized by the Medical Device Amendments of 1976 to the Food, Drug, and Cosmetic Act, Sections 513 through 521 of the act (Public Law 94-295), while the regulation of electronic products that emit electromagnetic or sonic radiation is authorized by the Public Health Service Act as amended by the Radiation Control for Health and Safety Act of 1968 (Public Law 90-602). Radiation-emitting electronic products that are also medical devices are regulated under authority of the Medical Device Amendments of 1976 to the Food, Drug, and Cosmetic Act as well.

CDRH responsibilities for control of medical sources of ionizing and nonionizing electromagnetic radiations sound vibrations (including ultrasound) and other physical hazards are critical. Although the following disclaimer refers largely to ionizing radiation, similar or identical approaches and concepts apply to risk assessment (and risk management) of other radiation types. Concern about inadequacies in the scientific data base and about the risk assessment process itself are also similar, though they are presented here in terms of ionizing radiation.

Organizational Placement

The CDRH within FDA is responsible for evaluating the safety and effectiveness of medical devices and radiation-emitting electronic products. Professional staff personnel with responsibilities for assessing the risks of these devices are located in the Office of Device Evaluation and the Office of Science and Technology.

Agenda Setting

Applications for Postamendment Devices. There are three types of applications for new devices: premarket notification (510[k]), investigational device exemption applications (IDE), and premarket approval applications (PMAs). Manufacturers use 510(k) applications to establish that a new device is substantially equivalent to a device on the market prior to enactment of the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act. IDEs are used to request permission for the use of a new device that has not met the test of substantial equivalence in clinical tests performed to establish its safety and effectiveness. PMAs are used to present results of tests demonstrating that a device is safe and effective and that any risk posed by a new device is outweighed by its benefits when it is used as intended and recommended by the manufacturer. Applications of each type are usually processed in order of their receipt by the agency. As in the other FDA Centers, there are limits on the time the CDRH may take to respond to applications for the approval of new products. CDRH has 30 days to respond to IDEs, 90 days to respond to 510(k) applications, and 180 days to PMAs. However, the deadlines for FDA response may be extended if an application is deficient and CDRH requests more information from the sponsor.

Preamendment Devices. The CDRH is continuing the classification process for devices marketed prior to 1976. Medical devices are classified into three groups (classes I, II, and III) based on such factors as the potential health complications associated with use of a device and the number of people exposed. Class III devices are those that pose the greatest potential public health risk and require submission of PMA.

Risk Assessment Methods

Medical Devices. Approval of a PMA for a medical device requires presentation of scientific evidence by the manufacturer, including evidence from preclinical testing and clinical trials, that any risk posed by the use of the device is outweighed by the expected medical benefits when it is used as intended by the manufacturer.

Preclinical studies are used in the hazard identification and hazard characterization phases of the assessment of potential adverse health effects associated with the use of medical devices. Animal toxicology and performance studies initially test the safety and effectiveness of a device. Preclinical studies may include material science and engineering laboratory studies, such as electrochemical and structural tests for implanted devices or emissions studies for radiological devices. Exposure characterization occurs primarily through the collection of patient demographic information and evaluation in followup studies.

In the risk determination phase of the assessment, PMAS are presented to a panel of experts who review scientific data on the product and make recommendations to the commissioner. Devices may be accorded restricted approval, with marketing and distribution limited to individuals and settings that can assure safe and effective use of the product.

Approval of a 510(k) application is based on the demonstration of substantial equivalence of the device to a product marketed prior to enactment of the device amendments, whereas approval of a PMA requires proof that the benefits of a device outweigh its risks when the device is used as directed by the manufacturer. The PMA generally includes both toxicological and human clinical trial studies, and may also include structural studies of the materials in the device.

FDA approval of IDEs permits the distribution of devices for study in clinical trials after acceptable margins of safety and effectiveness can be inferred from preclinical data. Safety may be determined through documentation and analysis of the nature and frequency of complications associated with the device using clinical and epidemiological studies. For example, clinical studies of a new orthopedic implant may use historical controls for comparison of safety and effectiveness. In contrast, some clinical studies used to support PMs must have concurrent controls.

Radiological Health. Public Law 90-602, the law regulating radiation aspects of electronic products, is not limited to medical devices, but is applicable to all types of electronic products, with the exception of specialized products under the purview of the Department of Defense (DOD). Thus, the FDA administers two statutes to regulate electronic products. The radiological health law regulates the manufacture of radiation-emitting products by providing product recall authority and the authority to promulgate performance standards, while the medical device law requires premarket approval when appropriate. Risk assessments performed on electronic devices must determine whether the devices meet the requirements of both laws.

The neodymium-yttrim-aluminum garnet (YAG) laser used or being investigated for use in a variety of surgical procedures varying from eye surgery to tumor excision is an example of a device that is regulated under both laws. Under the medical device law, the FDA assesses whether this laser is as safe and effective as other lasers used in a particular application or whether it is safe and effective for a new use. Under the radiological health law, the FDA determines whether the laser meets the Federal Laser Performance Standard and whether additional training is necessary for physicians to safely use this device.

Scientific Review

Scientific review of a risk assessment of a new device depends on the type of application. 510(k) applications are reviewed by the CDRH staff, and no further review takes place if the device is found to be substantially equivalent to a device that was in commercial distribution prior to enactment of the medical device amendment. If it is not found to be substantially equivalent, the device is placed in class III, and the application must be submitted as a PMA with all the appropriate preclinical and clinical testing unless the device is reclassified to a lower class. If clinical data are not available, an IDE may be requested. IDEs, like INDs for drugs, permit the distribution of devices for study in clinical trials after acceptable margins of safety and effectiveness are inferred from animal data in a review by the CDRH staff.

PMAs are first reviewed by the CDRH staff. If the new device passes their scrutiny, the review is sent to one of 11 standing outside panels that cover devices used in different medical specialties. Panels are composed of experts in various areas and include representatives from consumer and industry groups. Other experts can be brought ad hoc to assist the panel. Panel meetings are announced in the *Federal Register* and interested parties are allowed to make presentations. The recommendations of the statutory panels are advisory.

If a PMA is approved, a publicly available "Summary of Safety and Effectiveness" is prepared to explain the basis for approval, and a notice of the approval is published in the *Federal Register*. Objections to the approval may be filed during a thirty-day period, and the assessment may be reviewed again. If a PMA is denied, the CDRH publishes full reasons for its denial. The denial and the risk assessment may be appealed through in-house administrative hearings, independent review panels, and/or the courts.

Public Involvement

The formal mechanisms for public involvement in the risk assessment and regulatory process are similar to those described for other FDA Centers.

Description of Risk Assessment Reports

The "Summary of Safety and Effectiveness" that is prepared in response to each PMA that is submitted to the CDRH typically includes information from pertinent preclinical and clinical studies as well as indications and contraindications for use, alternative practices or procedures, and potential adverse health effects. For each major topic (e.g., preclinical toxicology, materials science, etc.), the CDRH states whether or not it believes the sponsor has presented adequate proof of safety and effectiveness. The CDRH also attempts to identify uncertainties in the data and subgroups of the population for which the results of the submitted studies may not apply.

Mechanisms for Forwarding Results for Policy Decisions

Summaries of safety and effectiveness are forwarded to the director of the Office of Device Evaluation for approval or denial. The director receives a packet of information containing a summary memorandum, a draft of the Summary Statement of Approval for public distribution, and background documents, including studies and correspondence.

Procedures for Disseminating Findings to the Public

As indicated above, a notice of the availability of the results of the risk assessment is published in the *Federal Register* following either approval or denial of a PMA. The risk assessment itself is available through the CDRH in the form of a Summary Statement of Approval.

Evaluation of Public Health Effects of Assessments

Established reporting procedures must be followed in accordance with the Medical Device Reporting regulation (MDR). All serious adverse effects must be reported to the FDA within five working days after they come to the attention of the manufacturer. These reports must be followed up with more detailed information within 15 days.

The FDA also receives reports of adverse experiences with medical and radiological devices from several voluntary reporting systems, including the Device Experience Network, the Government-Wide Quality Assurance Program, and the National Electronic Injury Surveillance System.

In approving a PMA, the CDRH may require postmarket surveillance. For orthopedic implants, for example, this may include a two, five, or ten-year follow-up study on a subset of the patient population that participated in the clinical trials. The sponsor must submit annual reports detailing all adverse effects associated with the use of the device.

Toxicological Research: NCTR

The mission of the National Center for Toxicological Research (NCTR) is to increase the scientific knowledge base concerning toxic substances. To meet this goal, the NCTR conducts studies, provides data in support of FDA research objectives, and supports research through interagency agreements with other governmental agencies. The NCTR also conducts research as the FDA's contribution to the NTP.

Mandate

The NCTR was established in 1971 under the auspices of the FDA by an executive order implemented by the President's Office of Science and Technology Policy (OSTP). The NCTR is charged with the responsibility to (1) investigate the toxic effects of low-dose, long-term exposure to chemicals; (2) develop methodology to investigate toxic effects of chemicals; (3) elucidate biological mechanisms of toxicity; and (4) provide improved methods for estimating human health effects from laboratory animal experiments. Although NCTR scientists have performed quantitative risk assessments containing all four assessment steps for specific compounds, the major role of the NCTR in health risk assessment is to provide information useful in the hazard identification and hazard characterization steps of the assessment process and to develop general methods to improve the accuracy of the risk assessments.

Organizational Placement

Of the five centers within the FDA, the NCTR is a focal point for toxicological research and risk assessment. Through interagency agreements, it also supports the toxicological research activities of other federal agencies such as the National Institute for Occupational Safety and Health (NIOSH), the NIH, including the National Cancer Institute (NCI), the USDA, the Consumer Product Safety Commission (CPSC), the DOD, and the EPA.

Agenda Setting

By the late 1970s, the NCTR was devoting considerable resources to the generation of chronic bioassay data and serving as a research center for developing and validating new toxicological tests. Priorities for toxicological testing were set by the other FDA Centers requiring information. Compounds were also assigned to NCTR for testing, through the NTP selection process (see Chapter 8).

In the early 1980s, NCTR began refocusing its resources on its original mission of enhancing methodologies in support of health risk assessment. Four broad research areas have been selected for intensive study: (1) assumptions underlying risk assessments, (2) modulating factors in toxicology, (3) biomarkers, and (4) reproductive and developmental toxicology. Biological detoxification mechanisms may be a fifth area of concentration in the future.

Risk Assessment Methods

Research at the NCTR is directed toward bridging the gaps among research conducted by universities and some government agencies, applied research occurring in some industrial laboratories, and established testing programs within the federal government. In addition, emphasis is placed on finding solutions to economically or socially important toxicology problems having a major impact on human health. An overall goal of the NCTR is to define and test the various assumptions and parameters involved in quantitative risk assessment, including both the biological and biometric aspects.

The NCTR provides support to the chemical testing programs of the NTP and thus promotes the hazard identification and hazard characterization phases of risk assessment. Although the NCTR is involved in chemical testing, the center's major research emphasis is on determining the basic mechanisms of toxicity in animals and developing data to aid in assessing the risk to human beings of toxic chemicals. Basic research activities of the NCTR focus on understanding how chemicals produce cellular injury or induce toxic changes in cells. Topics under current investigation include (1) the role of DNA damage and repair in chemically induced degenerative disease processes; (2) understanding the synergistic interaction between physical particles and chemical carcinogens; and (3) the role of oncogenes in both the development of, and the responses to, toxic action.

Another mission of the NCTR is improving extrapolation methods used to apply results from basic research and from animal models to the determination of potential human health risks. Like the basic research activities described above, this work is an important component of the hazard characterization phase of risk assessment.

Risk determination at the NCTR is generally conducted as part of consensus development workshops that focus on scientific aspects of critical issues in toxicology affecting public health or the economy.

Scientific Review

The NCTR's scientific review system is based on the size of the project. A small project (requiring less that 250 hours of work) is approved at the division director level. Mid-size projects (requiring up to 1,000 hours of work) or projects involving more than one division require final approval from the NCTR director. Large projects are subject to both internal and external review. Prior to the actual conduct of a large-scale study, the experimental protocol is reviewed three times: at the division level, by a panel of senior NCTR scientists, and by a panel of outside peer reviewers. Completed studies are reported in the NCTR report series, and many are also published in peer-reviewed journals.

Public Involvement

NCTR programs are reviewed by a seven-member Science Advisory Board, which includes a representative of the lay public.

Consensus workshops and other scientific meetings sponsored by the NCTR are generally open to the public, and all final reports are available to the public.

Description of Risk Assessment Reports

The NCTR's research results are released via technical reports, final reports, and manuscripts and abstracts. A technical report is usually one in a series of status reports to management on the same project, particularly one that requires extensive inquiry and several years of effort. Final reports generally present the results of completed work on a specific project or series of experiments that end that particular research endeavor at the NCTR. A typical final report includes a list of specific aims of the project and an executive summary, along with details of background, experimental methods, results and discussion, and references. An executive summary includes recommendations and overall observations concerning the project. Manuscripts and abstracts are submitted to appropriate scientific journals for publication.

Mechanisms for Forwarding Results for Policy Decisions

The NCTR does not make policy decisions based on risk assessment results, but sends the final report to the FDA center or other agency that requested a study. All of the raw data from the study are available on request.

Procedures for Disseminating Findings to the Public

Distribution of NCTR technical and final reports depends on the nature of the study. The typical distribution of an NCTR report includes intragovernment distribution to the Centers for Disease Control (CDC), the National Institute of Environmental Health Sciences (NIEHS), the FDA, the NIOSH, and other government sponsors, as well as special external release to science advisory board members, the scientific community as determined by the principal investigator or recommended by the NCTR staff, and public groups potentially impacted by the study.

Evaluation of Public Health Effects of Assessments

There is no formal mechanism within the NCTR to determine the extent and means by which the results of the reports are used and whether they have affected public health.

CASE STUDIES

D&C Green No. 6: CFSAN

On April 2, 1982, the FDA published a final rule (47FR4138) listing D&C Green No. 6 as a color additive for use in externally applied drugs and cosmetics. Much of the following discussion is based on information contained in this *Federal Register* notice.

D&C Green No. 6 was the first color additive approved under the FDA's Policy for Carcinogenic Trace Constituents of Food and Color Additives, referred to as the constituents policy. Constituents are defined to be nonfunctional chemicals present in a food or color additive. The Advance Notice of Proposed Rulemaking for this policy appeared in the *Federal Register* on the same day as the Final Rule for D&C Green No. 6. Under the constituents policy, additives with carcinogenic constituents may be approved if the additive as a whole is not carcinogenic and if it meets the "reasonable certainty of no harm" standard of the general safety clause.

The constituents policy approach requires a quantitative assessment of the risk posed by the carcinogenic constituent at levels likely to be encountered under the conditions of proposed use. The FDA argues that it can adequately determine the upper bound of (but not the most likely) carcinogenic risk to humans by using conservative assumptions and extrapolation procedures. This approach to regulation was used for D&C Green No. 6 because the chemical contains trace amounts of p-toluidine, an animal carcinogen. The FDA anticipates that, if the proposed constituents policy is ultimately approved, improved analytical capability and more extensive toxicity testing will lead to the evaluation of many additives.

Hazard Identification

In 1979, an FDA chemist reported that commercial preparations of D&C Green No. 6 might be contaminated by p-toluidine, which had recently been shown to be an animal carcinogen in a chronic animal bioassay conducted by the National Cancer Institute. The FDA asked the sponsors of D&C Green No. 6 to develop appropriate analytical methodology to detect the presence of p-toluidine in the additive. The sponsors developed such a method based on high-pressure liquid chromatography separation followed by ultraviolet light or fluorescence detection. Analysis of nine lots of D&C Green No. 6 for residual p-toluidine by this method demonstrated an average contamination level of 393 ppm (0.0393 percent) p-toluidine.

Hazard Characterization

In characterizing the hazard presented by the color additive, the FDA relied primarily on a lifetime skin-painting study, in which a 1 percent solution of D&C Green No. 6 in benzene was applied to mouse skin, because the safety of external uses alone was being evaluated. No significant adverse compound-related effects were observed.

When the FDA applied quantitative risk assessment techniques to the NCI bioassay data to evaluate the carcinogenic hazard caused by the p-toluidine impurity, it estimated an upper limit of potential hazard (and risk) for the group of animals showing the highest tumor incidence per unit dose. The FDA then applied two linear proportional extrapolation procedures to extrapolate the cancer incidence from the high dose used in the experiment to lower doses more commonly encountered by humans.

Exposure Characterization

The FDA calculated both a total population exposure and a maximum probable individual exposure to p-toluidine. The total population exposure was calculated by dividing the annual average production poundage of D&C Green No. 6 by the population of the United States, assuming the color additive contained 500 ppm p-toluidine. By this measure, exposure to p-toluidine in D&C Green No. 6 would be less than 0.006 μg/day/person, or if all the products were consumed by only 10 percent of the population, 0.06 μg/day/exposed person.

The maximum probable individual exposure to p-toluidine is more difficult to estimate because it depends on the concentration of p-toluidine (or of D&C Green No. 6) in each product, the amount and frequency of usage of each product, and the proportion of each product that actually enters the human body. For example, the FDA estimated that very little of the D&C Green No. 6 and p-toluidine in bath oils and hair preparations, two of its major uses, would come into contact with skin. The FDA did not calculate maximum probable individual exposure, but considered that only a small amount of the p-toluidine found in externally applied cosmetics and drugs would penetrate the skin and contribute to internal exposure.

The FDA concluded that for high users the lifetime-averaged individual external exposure to p-toluidine from the use of cosmetics and drugs with D&C Green No. 6 is no more than 0.1 μg/day and that internal exposure is substantially lower. Exposures to at least two other approved color additives which contained p-toluidine as a manufacturing impurity, but at lower levels than D&C Green No. 6, were considered in the risk determination.

Risk Determination

FDA scientists used a linear proportional model to estimate the upper 99 percent confidence limit on the cancer risk to male mice from lifetime oral exposure to 0.1 μg/day p-toluidine (the maximum probable individual exposure calculated previously). The risk was estimated to be not greater than 1 in 15 million. Because the FDA assumed that humans are not more sensitive to p-toluidine than male mice, this value was also taken as an upper limit of human hazard. Thus, the FDA concluded that the current usage of D&C Green No. 6 at the current contaminating levels of p-toluidine would result in less than one additional tumor in 15 million people. Furthermore, it concluded that additional exposure to p-toluidine from other color additives would not affect its evaluation and that the use of D&C Green No. 6 in externally applied drugs and cosmetics is safe.

6-Methylcoumarin: CFSAN

The synthetic chemical 6-methylcoumarin (6MC) was introduced as a fragrance ingredient in a variety of cosmetics and toiletries in the United States in 1920. In February 1978, a report identified 6MC in some sunscreens and suntanning preparations as a cause of serious, disabling skin and systemic disorders in a significant number of users. Subsequent tests showed it to be a potent photocontact allergen; when 6MC on skin is exposed to sunlight, it may induce a strong allergic reaction.

In December 1978, the FDA sent telegrams to manufacturers and distributors of suntan and sunscreen preparations requesting that they voluntarily recall from the market all preparations containing 6MC. The FDA also proposed to ban 6MC from all cosmetics and topical drugs. However, fragrance suppliers had already begun to warn bulk chemical buyers that the material was under review by the FDA for its photoallergic potential, and the prefume industry began phasing 6MC out of its formulations soon after the first recognition of the problem in February 1978.

Following the FDA telegrams and other pressure, fragrance suppliers stopped offering 6MC as an ingredient for cosmetic products. Since it then appeared that no regulation was needed, none was issued.

Hazard Identification

Consumers and health professionals brought the link between suntan preparations and serious skin disorders to the FDA's attention. Plough Corporation sponsored the sunscreen studies following numerous consumer complaints.

Identification of the causative agent was complicated. Sometimes the reaction occurred on first exposure, leading to the suspicion that the agent was phototoxic. Testing showed that the sunscreening agent used in the product was phototoxic; however, changing the sunscreen did not fully resolve the problem. Clinically, only a small portion of the suntanning preparation users had an adverse reaction implying an allergy. However, phototesting by conventional methods gave inconsistent and inconclusive results. Furthermore, it was believed at that time that only phototoxic materials could produce photoallergic reactions. Once the sunscreen was removed, there were no phototoxic agents in the suntanning preparation. Eventually, investigators outside of the FDA identified 6MC as the problem ingredient. In February 1978, the Research Institute of the Fragrance Manufacturers issued a report associating 6MC with the adverse skin reactions.

Hazard Characterization

The FDA relied heavily on a new test for photocontact allergens, the photomaximization assay, in its assessment of the risks associated with 6MC. In a preliminary study, 5 percent 6MC in ethanol solution was applied to patches on the backs of 24 volunteers in a conventional photopatch test for sensitivity to 6MC. Six hours later, the patches were exposed to ultraviolet light from a solar simulator. Two of the volunteers developed an itchy, vesicular reaction that spread beyond the exposure site and had features of a photocontact allergy except that it occurred after the first application of 6MC.

In a second test, the photomaximization assay, 10 college students who had tested negatively to 6MC in the conventional photopatch test were exposed to 6MC by the application of a hydrophilic ointment containing 5 percent 6MC to a square patch on their backs. The proprietary suntanning preparation was tested at the same time using the same protocol. Twenty-four hours later, the patches were exposed to light from a solar simulator. After 48 hours, similar applications of 6MC and the suntanning product were made to the same sites, which were again exposed to a solar simulator 24 hours later. After six repetitions of the sequence, six of the ten subjects develoved photocontact allergic reactions to 6MC ranging from intense erythema and edema to a vesicular spreading dermatitis. Five of these six subjects developed similar responses to the suntanning preparation.

This high rate of response to 6MC led the researchers to conclude that 6MC is a potent photocontact allergen. They also concluded that the two volunteers who exhibited strong reactions to 6MC upon first exposure must have been sensitized earlier by small amounts of 6MC present in toiletries and cosmetics (typically 0.001 percent to 0.04 percent of finished products).

Exposure Characterization

Although the FDA did not have sufficient data available to conduct an exposure characterization, its telegrams to fragrance suppliers and suntan preparation manufacturers requesting recall also requested information that would help it prepare an exposure assessment of 6MC. The FDA received the names of products containing 6MC and percent concentrations from suntan preparation manufacturers. From fragrance manufacturers, the FDA requested a list of customers who had received perfumes or other materials containing 6MC within the last three years. This information served to identify other cosmetics and topical drugs that contained 6MC.

Risk Determination

The FDA performed its own internal risk determination for 6MC; no public document has been released. A synopsis of the risk determination indicates some controversy about the concentration of 6MC required to elicit the photoallergic response. Since the data indicate that the response can be generated at concentrations as low as 0.001 to 0.04 percent, it appears that no safe concentrations for final products could be set.

Diethylstilbestrol: CVM

The approval and subsequent withdrawal of approval of NADAs for diethylstilbestrol (DES) took place over the course of 30 years. The legal history and some of the scientific basis of these regulatory decisions are summarized in the commissioner's decision to withdraw approval of NADAs for DES, published in the *Federal Register* on September 21, 1979.

DES is a member of a class of compounds known as stilbenes. Although the chemical structure of DES differs from the steroidal hormones such as estrogens, it has some biological properties similar to estrogenic hormones. When the FDA first approved DES for human use in 1941 it was widely used for relief from menopausal disorders. In 1949, FDA approved the use of DES for the prevention of threatened (natural) abortion. Hundreds of thousands of women received DES for this purpose until the FDA banned its use for pregnant women in 1972. DES remains in use as a human drug for some antineoplastic uses and as an estrogen supplement.

The first veterinary use of DES, as a growth promotant in chickens, was approved by the FDA in 1947. A pellet of DES was implanted in the necks of young roosters to promote fast weight gain and produced plump capons. Necks containing the pellet were not to be used for human food. In 1954, the FDA extended its approval of DES (under Section 505 of the Food, Drug, and Cosmetic Act) to include its use as a feed additive to promote growth in cattle. It was subsequently approved for use as an ear implant to promote growth in cattle and for use as both a feed additive and ear implant to promote growth in sheep.

The FDA approval of DES in animal feeds and implants was based on data that demonstrated that 48 hours after withdrawal no DES residues could be detected in edible tissue of livestock by analytic methods in use at that time. However, the mouse uterine assay used to detect DES can detect estrogenic effects only if an estrogenic compound is present in concentrations of potency similar to DES (but not necessarily DES) at or above 2 ppb. The paper chromatography assay that followed specifically detected DES, but only at concentrations above 10 ppb.

The Delaney clause, enacted in 1958, prevented additional approvals for DES because it was found to induce cancer in animals. In 1962, however, Congress amended the Delaney clause with the "DES exception," which again allowed carcinogenic drugs to be used in animal production if they did not cause harm to the animals and if no residues were found to remain in the edible tissue, as determined by an FDA-approved method of detection. In 1963, the FDA implemented this congressional mandate in food additive regulations providing for the use of DES in food animals and establishing the immature mouse uterine assay and paper chromatography assay as the approved methods of residue detection. The first three NADAs for DES were granted prior to the enactment of the Delaney clause but before the DES exception was enacted in 1962.

More sensitive analytical techniques available in the early 1970s allowed the detection of DES in the edible tissues of animals at levels below the sensitivity of the mouse uterine assay; that is, when DES was present at concentrations less than 2 to 10 ppb. The FDA published notices of an opportunity for hearings on the proposed withdrawal of approval of NADAs for DES feed additive premixes (March 1972) and implants (June 1972). In August 1972, FDA denied hearings on DES feed premixes on the ground that holders of NADAs failed to demonstrate the presence of genuine and substantial issues of fact, and approval of DES premixes was withdrawn. The FDA withdrew approval of NADAs for DES implants in April 1973 after denying a hearing for similar reasons. The NADAs were reinstated, however, after the U.S. Court of Appeals reversed the FDA's actions on the procedural ground that it was necessary to hold public hearings.

In March 1974, the FDA proposed to revoke the approved methods of analysis for DES on the grounds that this method failed the criteria of accuracy, sensitivity, and specificity. The FDA responded to comments on this proposal in January 1976 and issued a notice of opportunity for hearing. At the request of manufacturing parties, a full evidentiary hearing was held in 1977 before an adminstrative law judge.

The administrative law judge concluded (September 1978) that approval of NADAs for DES must be withdrawn. All parties appealed this decision to the commissioner of the FDA. The commissioner's decision (September 21, 1979, *Federal Register*) supported most of the findings of fact and conclusions of law of the administrative law judge. Again, the approval of NADAs for DES were ordered to be withdrawn with an effective date of October 31, 1979.

The manufacturing parties appealed the commissioner's decisions to the U.S. Court of Appeals, which subsequently upheld the commissioner's decision.

Hazard Identification

For animal drugs such as DES, hazard identification begins with the manufacturer's submission of an NADA. Before an NADA is approved, the manufacturer must submit enough toxicology data to demonstrate "safety" for both animals and humans.

Prior to the approval of DES by the FDA, tests in laboratory animals had indicated that DES might be carcinogenic. Nevertheless, DES residues were not measurable by available methods of detection when DES was withdrawn at a specified time prior to slaughter. This allowed the determination that DES was "safe" to use under specific conditions. In the early 1970s, however, two studies by USDA scientists indicated that DES remained in the tissues of cattle and sheep even if DES was withdrawn as a feed additive or the pellets implanted at the prescribed time prior to slaughter.

Hazard Characterization

The first evidence that DES was carcinogenic in humans was a report in April 1971 that the use of DES by pregnant women to prevent miscarriage was followed by increased risk of clear cell adenocarcinoma of the vaginia, a rare form of vaginal cancer, in daughters born of the women treated during that pregnancy. Later studies showed that DES is also a teratogen. "DES daughters" have a significantly higher incidence of certain benign abnormalities in the vaginal tract than matched controls. Effects on the genital tract of male offspring are also associated with DES intake by pregnant mothers. In mice, DES treatment of dams causes loss of fertility of female progeny. DES diphosphate, which can be hydrolyzed to DES, is mutagenic in mouse bone marrow cells. Production of trisomes has been detected in mice whose dams were treated with DES diphosphate.

During the regulatory proceedings on the withdrawal of DES NADAs, both industry and FDA scientists tried to assess the risk to humans of chronic exposure to low doses of DES. Industry scientists based their risk estimates on human data obtained from studies of DES daughters and included the following assumptions: (1) the only cancer that DES causes in women is vaginal adenocarcinoma in the daughters of DES-exposed mothers; (2) there is a linear dose-response for DES from the lowest DES dose that has been associated with vaginal adenocarcinoma to lower exposure levels; (3) the risk of lifetime exposure to DES is identical to the risk of exposure of the child to DES during the mother's pregnancy; and (4) the incidence of vaginal adenocarcinoma associated with DES exposure in utero is known. Industry scientists concluded that consumptions of meat products containing DES would be expected to result in a cancer risk no greater than 3 in 100 million.

In contrast, FDA scientists based their hazard characterization and subsequent quantitative risk assessment on lifetime animal toxicity studies. They applied a linear extrapolation model to the upper 99 percent confidence limit on the tumor incidence data to estimate the tumor response at lower doses of DES. They calculated that in laboratory animals the upper limit of risk from 1 part per trillion DES in the diet was less than 1 cancer in 1 million exposed.

Exposure Characterization

The characterization of human exposure to DES in animal products can be divided into steps: (1) measurement of DES present in meat products and (2) estimation of the per capita consumption of meat products in the United States. In the late 1960s and early 1970s, the USDA residue monitoring program began measuring DES by liquid chromatography/mass spectrometry (glc/ms) rather than the FDA-approved assay. Among other advantages, use of glc/ms allows the detection of DES at 0.5 ppb, compared with the 2 ppb level of detection of the mouse assay. By testing randomly selected samples of beef and sheep livers in the glc/ms assay, the USDA was able to estimate at the 95 percent confidence level that 0.2 to 2.5 percent of the animals slaughtered in the mid-1970s had DES residues above 0.5 ppb in their livers. No estimates of meat intake were developed as a part of the FDA staff assessment.

Risk Determination

Industry scientists extrapolated data on the human DES daughters study discussed above to estimate that the lifetime risk of cancer from DES is 3 in 100 million. Assuming that there are 4 million births per year in the U.S., this risk is equivalent to 1 cancer every 8 years. This calculation again assumes that DES induces only vaginal cancer, and only when administered transplacentally. As mentioned in the hazard characterization section, FDA scientists estimated that the lifetime risk to laboratory animals of 1 part per trillion of DES in the diet was 1 cancer in 1 million animals.

The decision of the FDA commissioner (September 21, 1979) dimissed both quantitative risk assessments on grounds that DES is a carcinogen when ingested by human beings and that there is no known no-effect level.

Moxalactam Disodium: CDB

Moxalactam disodium, the first oxa-beta-lactam broad spectrum antibiotic, is generally classified with the "third generation" cephalosporins. It was approved and first marketed in November 1981 for treatment of lower respiratory, intra-abdominal, skin and skin structure, urinary tract, central nervous system, and bone and joint infections as well as bacterial septicemia caused by susceptible strains of microorganisms designated in the labeling.

When postmarketing surveillance revealed a much higher risk of moxalactam-induced interference with blood coagulation than was expected from clinical trial data, FDA reviewers agreed that the drug labeling should be revised. The FDA asked the manufacturer (Eli Lilly Company) to update and expand its labeling section about the bleeding phenomena that occur in association with moxalactam therapy, and to highlight the problem with a box warning. The FDA and Lilly agreed to decrease the recommended highest dose to one that had been found to be equally effective, to advise administration of prophylactic vitamin K in conjunction with moxalactam, and to notify physicians about the coagulopathy problem and about these labeling changes in a "Dear Doctor" letter. After negotiations, the FDA and Lilly agreed on wording for the revised label, and the FDA formally announced the required changes in July 1983.

The FDA is continuing its review of the safety of and appropriate uses for moxalactam disodium. In September 1984, the FDA Anti-Infective Drugs Advisory Committee discussed further labeling changes to limit the use of moxalactam to serious infections.

The FDA review of the effects of moxalactam disodium triggered review actions in other countries, notably the Federal Republic of Germany, which held its own hearings and ruled that a labeling change recommending moxalactum disodium only for serious or life-threatening infections would be required. This was later changed to serious infections, which is consistent with German labeling for all third-generation cephalosporins having two specific side chains in their chemical structure. The new German ruling, in particular the version of the label indicating use in the case of serious, life-threatening infections, was noted by the FDA at its September 1984 Advisory Committee meeting, and influenced the recommendation to limit use in the United States to cases of serious infections.

Hazard Identification

Moxalactam disodium, like all other drugs regulated by the FDA through the NDA process, was subject to extensive clinical testing prior to approval. During clinical trials, moxalactam was found to be associated with hypothrombinemia, platelet dysfunction, and, very rarely, immune-mediated thrombocytopenia. A total of 2.5

percent of clinical trial patients treated for four days or more experienced a bleeding event, most of which were serious. Such bleeding disorders are not frequently reported for drugs with chemical structures similar to moxalactam disodium.

After moxalactam entered the marketplace, bleeding disorder reports were received either directly from physicians through the FDA's spontaneous adverse drug reporting system or from Lilly. According to the conditions of an NDA, the pharmaceutical manufacturer must promptly submit to the FDA any adverse reaction reports that it receives. The increased risk was also reported by publications in the medical literature.

Hazard Characterization

The FDA used the computerized Adverse Drug Reactions files to analyze spontaneous reports of adverse effects associated with moxalactam disodium and to compare them with those for eight other anti-infective drugs. Reports of hemorrhage, elevated prothrombin time, increased bleeding time, and other coagulation disorders were more frequent for moxalactam than for the other drugs. It was noted, however, that Lilly generally submits more adverse reaction reports to the FDA on all of its drugs than do other manufacturers.

To further characterize the hazard of moxalactam disodium, the FDA reviewed reports of the mechanism by which the drug causes excessive bleeding. The exact mechanism is controversial, but moxalactam appears to eliminate vitamin-K-producing microorganisms in the gastrointestinal flora. Vitamin K is an important component of the normal blood clotting process and can be used to treat hypoprothrombinemia. Moxalactam also induces a significant suppression of adenosine diphosphate-induced platelet aggregation. It appears that this occurs in vivo by perturbing the platelet membrane, thus making receptors unavailable. Inhibition of platelet function is dose-dependent and can generally be avoided by limiting the moxalactam dosage to 4 grams per day.

Exposure Characterization

Reports to the FDA from the manufacturer show that approximately 344,000 patients were treated with moxalactam in the United States between November 1981, when moxalactam entered the marketplace and February 1983, when the adverse report data were summarized. Since moxalactam is usually selected when treatment of difficult infections is needed, some of the bleeding events may have been due to the infection itself or to the complications of the underlying diseases rather than to the moxalactam. It is difficult or impossible to rule out these cases.

Risk Determination

As shown by the information in the Adverse Drug Reactions File, moxalactam disodium is associated with an increased risk of bleeding events. However, the risk of the bleeding might be reduced by using the lowest dose required to treat the infection and by the concomitant administration of vitamin K. These means of reducing the risk were communicated to physicians by changes in the labeling and in a "Dear Doctor" letter. The changes were negotiated between the FDA and Lilly; the Anti-infective Drugs Advisory Committee was not involved in the earlier action.

In its September 1984 meeting, the Anti-infective Drugs Advisory Committee was asked to consider additional, but controversial, information about the mechanism of moxalactam-associated bleeding, and was advised about the new German labeling requirement that moxalactam was to be used only for serious infections. Part of the advisory committee discussion involved a consideration of the controversial theory that the presence of the N-methyl-tetrazolethyl side chain in the moxalactam molecule was a factor in the coagulopathy events. This side chain is present in several antibiotics, all of which might be subject to bleeding events that might be prevented by the administration of vitamin K. Moxalactam is considered to be an important and useful antibiotic because of its potent activity against microorganisms causing certain serious, difficult-to-treat infections, and because it is effective in treating meningitis. Doses recommended in the revised labeling are effective for moxalactam's indications.

Committee members agreed that the box warning was adequate. The committee recommended that the labeling used in Germany, which recommends moxalactam for "serious" infections, might also be appropriate in the United States. Other drugs that do not expose patients to the risk of bleeding are available for the treatment of less serious infections.

The committee's recommendation is under consideration by the FDA's Division of Anti-infective Drugs.

Orthopedic Implants: CDRH

Certain orthopedic implants are subject to FDA premarket approval under the statutory authority of the Medical Device

Amendments of 1976. The safety and effectiveness assessment conducted for the PMA of the Porocoat© Modified Austin-Moore Total Hip Prosthesis illustrates the process that an orthopedic implant must undergo to obtain FDA approval.

In 1977, the FDA received an application for the prosthesis medical device now known as the Porocoat© Modified Austin-Moore Total Hip Prosthesis. The manufacturer (Medishield, Inc.) did not indicate that the device differed from devices then on the market, and the FDA approved the application under the 510(k) approval process. In 1980, the FDA became aware that this device had a porous, rather than a smooth, surface and that the DePuy®, Inc., Division of Boehringer Mannheim Company was offering the device for sale. In 1981, the FDA withdrew approval under the 510(k) permit and notified the manufacturer that it must submit either an IDE or a PMA for the device. DePuy® opted to submit a PMA under the condition that it could continue to supply the device to physicians having experience with its use (13 physicians) during the application process.

Hazard Identification

The PMA included both manufacturer-sponsored studies and a review of the world's literature on topics pertinent to the innovative features of the device, including laboratory, animal, and clinical data on the safety and effectiveness of the hip prosthesis. Because the device had an innovative porous coating, the application included data regarding the mechanical and bone tissue ingrowth properties of the coating. Biocompatibility studies were not included because the alloy used for the coating had been in use for 20 years; only the surface features were new.

Laboratory studies of the stability and strength of the materials needed to make the implant were designed to determine whether the porous surface would stand up to expected strains and stresses of everyday use. Porocoated© rods were implanted in dogs to examine bone tissue ingrowth properties and tensile strength of the new coating, and to test various modifications of the new material in order to improve fixation of the implants. Surgical methods for increasing implant fixation were also developed using animal models.

Hazard Characterization

The safety of the total hip prosthesis was evaluated from the postoperative results of 270 patients. Most of these patients (211 out of 270) were also evaluated at least once postoperatively for pain relief, mobility, and functional restoration; almost half of these (101 out of 211) were followed for two years or longer.

The manufacturer compared the incidence of selected complications with estimates from nine retrospective control groups. The patient populations were matched by three known risk factors—age, weight, and diagnosis. The manufacturer pooled data across all study patients for whom a postoperative complication could have been reported, and found, in agreement with the FDA, that in comparison to selected control groups the modified hip prosthesis appeared to lead to significantly greater incidence of late/deep infection, femoral loosening, revision, dislocation, and death. On the other hand, this hip prosthesis also appeared to lead to significantly fewer incidences of thromboplebitis, pulmonary embolism, hematoma formation, ectopic bone formation, and myositis ossificans. The FDA also noted that despite the matching, patients receiving the Porocoat© Hip Prosthesis might have differed from those receiving more conventional hip prostheses, so that the observed differences in complication rates might not reflect cause and effect.

The sponsor also compared scores for pain relief and restoration of function with those of designated controls, using several different scales developed for these parameters. The Porocoat© Hip Prosthesis scored worse than the controls on some of the scales and better on others.

Exposure Characterization

The Porocoat© Hip Prosthesis is designed to be implanted in selected patients with osteoarthrosis or rheumatoid arthritis, but no estimate was made of the number of hips that would be implanted.

Risk Determination

The Orthopedic Device Section of the Surgical and Rehabilitation Devices Panel performed the risk determination, and FDA staff reviewed its conclusions. Having concluded that, on balance, the Porocoat© Hip Prosthesis worked as well at the end of two years as others on the market, the panel recommended that the Porocoat© Modified Austin-Moore Total Hip Prosthesis be approved for marketing subject to several conditions, including precautionary statements, reduced indications for use, and continued surveillance for five years of patients who had already received implants.

The FDA agreed with most of the panel's recommendations, including all those just cited. In a letter to the manufacturer, the FDA approved the device subject to the conditions that the labeling be modified, postmarket surveillance be conducted, and adverse reactions and device defects be reported within 10 days following the date when the manufacturer becomes aware of the reaction. The FDA also required submission of annual postapproval reports containing summaries of reports in the scientific literature involving the device, unpublished reports of all studies of the device, written promotional material, and description of changes in the device not previously submitted in a PMA supplement.

Chapter 7

NATIONAL INSTITUTES OF HEALTH

The primary mission of the National Institutes of Health (NIH) is to discover new biomedical knowledge for use in the prevention, diagnosis, treatment, and cure of disease and disability. In pursuit of this mission, the NIH supports biomedical and behavioral research in the United States and abroad, conducts research in its own laboratories, and promotes the acquisition and dissemination of new medical knowledge. Many of the research findings developed by NIH institutes ultimately contribute to health risk assessment. The Agency Overview section of this chapter discusses general procedures and policies related to ongoing health risk assessment activities within the separate NIH institutes, as well as trans-NIH programs that include risk assessment activities, such as review of recombinant DNA research, consensus development conferences, and protection of human subjects of research.

AGENCY OVERVIEW

NIH Research and Risk Assessment: NIH

Each of the NIH institutes has activities important to determining health risks. Because they are all founded in the research enterprise and the approaches do not vary remarkably from institute to institute, only a generic discussion follows.

Mandate

Section 301 of the Public Health Service Act (42 U.S.C. 241) provides the statutory basis for NIH research activities. The broad mandate of the NIH is "to improve the health of the American public." Two of the 11 institutes within the NIH have additional statutory authority that relates to their research activities: the National Cancer Institute (NCI) under Title IV, Part A (42 U.S.C. 289) and the National Heart, Lung, and Blood Institute (NHLBI) under Title IVPart B (42 U.S.C. 287i).

Organizational Placement

The NIH is comprised of 14 bureaus, institutes, or divisions (BIDs), 12 of which have extramural granting programs:

- National Cancer Institute (NCI)
- National Eye Institute (NEI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute on Aging (NIA)
- National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Dental Research (NIDR)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute of General Medical Sciences (NIGMS)
- National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)
- Division of Research Resources (DRR)

Agenda Setting

In general, funding priorities for grants supported by the extramural research programs of the various NIH institutes are determined first by an evaluation of scientific merit by the assigned "initial review group" of the NIH's Division of Research Grants (DRG). Grant applications for support of research are approved or disapproved on the basis of scientific merit, relevance, and the investigator's capabilities. Approved grants are assigned a priority score for funding. The agenda for extramural research support is thus determined in part by the interests and abilities of outside scientists who apply to the NIH for research support. Each of the institutes also fosters research in specific areas that have been identified by institute staff and outside advisory groups as scientifically promising or of significant public health importance. The primary mechanism for generating research relevant to institute program priorities is through the use of Requests for Applications

(RFAs) and Cooperative Agreements, while support for multidisciplinary funding mechanisms such as program project grants or specialized research centers is allocated by each institute on the basis of available monies.

The intramural research program for each institute except the NCI is determined by the scientific director of the institute in concert with the institute director. Decisions take account of reviews of each branch, laboratory, or section, conducted by a Board of Scientific Counselors at least every four years. The board evaluates the total activity of the branch, laboratory, or section under review, including the scientific personnel staff working on a project as well as of the project itself, in terms of the quality of science being accomplished and peer recognition. The evaluations, which provide the basis for decisions concerning promotions as well as for program setting, are submitted to the scientific director, the deputy director of intramural research, and the office of the director.

Risk Assessment Methods

The level of involvement in health risk assessment activities varies from one NIH institute to another. The NCI and the NIEHS are the most committed to quantitative studies relevant to health risk assessment, while the most prevalent health risk assessment activity supported by the various institutes is that of identifying and characterizing the causes of disease. Ranging from basic biochemical investigations conducted in vitro to controlled clinical trials in humans, the studies and experimental methods used by each institute may be characterized as follows:

National Cancer Institute. The NCI conducts risk assessment activities such as (1) epidemiologic studies to delineate high-risk groups and individuals and to identify etiologic factors for cancer; (2) studies of cancer risk from low-level exposure to ionizing or nonionizing radiation; and (3) studies to identify occupational and environmental causes of cancer. Hazard characterization activities include (1) investigations using cultured human epithelial cells and tissues to study both the mechanisms of carcinogenesis and host factors that determine susceptibility; (2) research concerning the role of tumor initiators, promoters, and cocarcinogens in cancer risk; (3) combined laboratory and epidemiologic studies of cancer risk; and (4) investigations into the health risks of cancer treatments such as ionizing radiation and cytotoxic and immunosuppressive chemotherapeutic agents.

National Eye Institute. The NEI emphasizes the identification of genetic, environmental, racial, physiologic, dietetic, occupational, and lifestyle factors associated with the development or recurrence of eye diseases through laboratory, clinical, and epidemiological investigations. NEI conducts epidemiologic research aimed at identifying risk factors underlying senile macular degeneration, diabetic retinopathy, senile cataract, glaucoma, and other important causes of visual impairment and blindness. Examples of hazard characterization activities include clinical trials that assess the risks and benefits of various treatments for eye disorders.

National Heart, Lung, and Blood Institute. The NHLBI conducts and supports fundamental research on the heart, lungs, blood vessels, blood, and diseases that affect them. The NHLBI is involved mainly in hazard (or risk factor) identification and characterization through epidemiologic studies, risk factor reduction studies, and basic research on cardiovascular functions. Examples of these activities include (1) the Framingham and Honolulu heart studies, which provided population distributions of high density lipoprotein (HDL) cholesterol in relation to other heart disease risk factors; (2) the Multiple Risk Factor Intervention Trial (MR-FIT), which was aimed at examining the effects of modifying risk factors such as elevated blood cholesterol, elevated blood pressure, and cigarette smoking on the frequency of occurrence of coronary heart disease (see below); (3) the Coronary Primary Prevention Trial (CPPT), which was designed to determine whether reduction of cholesterol by drug therapy would reduce coronary heart disease (see below); and (4) in vitro studies demonstrating abnormal cation movement in the red cells of patients with essential hypertension.

National Institute on Aging. The NIA conducts fundamental research on the biomedical, social, and behavioral components of the aging process and the special problems and needs of older people. Many NIA studies identify and characterize risk factors through epidemiological and behavioral sciences approaches. NIA hazard identification research includes prospective and follow-up studies examining the effects of smoking, drug and alcohol use, eating behaviors, blood pressure, and exercise on disease prevention, health maintenance, morbidity, health services utilization, and mortality. Hazard characterization studies deal with the independent and joint effects of specific life styles, social support and stress, technological and occupational change, and other biopsychological, behavioral, and societal factors in age-related changes in health and functioning. These studies examine such outcomes as osteoporosis, urinary incontinence, and memory loss. They include investigation of the etiology, management, and natural history of age-related nervous system disorders, such as Alzheimer's disease, and the effects of aging on the nervous system. Other studies are examining the formation of health attitudes and behaviors, as well as socio-environmental interventions for reversing or alleviating old age disabilities.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. The NIADDK conducts basic research into the cause and pathophysiology of those diseases related to arthritis, the musculoskeletal structure, bone and skin, the endocrine system, the digestive tract, and the urogenital tract for which the causes are unknown or poorly defined. NIADDK research involves primarily hazard identification and characterization. Hazard identification activities include (1) research in basic and clinical nutrition to advance knowledge about the functions and requirements of nutrients in the body and the relationship of diet and nutrients to health and disease; basic, clinical, and epidemiological studies of the etiology and pathology of arthritis, diabetes, musculoskeletal, skin, endocrinologic, metabolic, digestive, kidney, and hematologic diseases, with emphasis on causative, genetic, and environmental factors; and (2) studies to identify markers that characterize individuals predisposed to these disorders. An example of risk characterization activities is epidemiological research geared toward clarifying the risk factors for the development of analgesic nephropathy, a condition associated with abuse of over-the-counter preparations containing combinations of analgesics (see below).

National Institute of Allergy and Infectious Diseases. The NIAID conducts and supports research contributing to a better understanding of the causes of allergic, immunologic, and infectious diseases and to the development of better means of preventing, diagnosing, and treating such illnesses. Studies in these broad areas emphasize hazard (risk factor) identification and characterization through epidemiological studies and clinical trials. Such activities include (1) a cohort study of homosexual men at risk of acquiring AIDS; (2) studies to identify the etiologic agents of Lyme disease and microbial enteric diseases; and (3) clinical trials aimed at evaluating viral vaccines, bacterial vaccines, and antivirals.

National Institute of Child Health and Human Development. The NICHD conducts basic research into the reproductive, developmental, and behavioral processes that influence the health of children, adults, families, and populations. Risk assessment activities at NICHD focus on risk factor identification through epidemiological studies and clinical trials including (1) investigations of the causes of prematurity, low birth weight, birth defects, and mental retardation; (2) research to identify behavioral antecedents of habits harmful to health in childhood; and (3) metabolic, genetic, nutritional, and immunologic antecedents to disease and disability. NICHD also conducts research on the effects of smoking, over-the-counter drug use, and other environmental substances on fetal development as well as research on new and improved contraceptives and on contraceptive safety.

National Institute of Dental Research. The NIDR conducts basic research into the causes, prevention, diagnosis, and treatment of oral disease. NIDR contributions to health risk assessment involve mainly risk factor identification and characterization through epidemiological studies, clinical studies, and animal studies. An example of NIDR hazard identification and characterization activities is its work to elucidate the role of genetics and teratogens in congenital craniofacial anomalies.

National Institute of Environmental Health Sciences. The NIEHS is involved in a variety of research activities related to the process of risk assessment. One of the major research foci of the institute is the identification and characterization of environmentally based problems that could ultimately pose a hazard to human health or well-being. This research often involves the investigation of mechanisms of chemical toxicity and the biological effects resulting from exposure to various environmental substances such as mercury, vinyl chloride, sulfuric acid mist, kepone, auto exhaust, pesticides, food additives, aerosols, nitrosol compounds, and occupational chemicals (e.g., benzene, butadiene, and methylene chloride). Special emphasis is also placed on the development of improved techniques (1) for understanding the mechanisms of toxicity of environmental and occupational hazards; (2) for detecting and quantifying exposures to low-level environmental pollutants and the acute or chronic effects that such exposures can produce; and (3) for estimating the risks of cancer and other chronic diseases in humans using epidemiological or laboratory-based data. Institute research also generates a wide range of experimental and epidemiologic data that are used by other agencies in the quantitative estimation of human health risks. Through these basic and applied research activities, the NIEHS helps provide the scientific information base and methodological procedures used by regulatory agencies concerned with controlling environmental hazards.

National Institute of Neurological and Communicative Disor-

ders and Stroke. "Health risk assessment" (a term largely implied and not explicitly used by the Institute) is an implicit ingredient of the totality of NINCDS prevention-focused research which is designed to (1) identify risk factors—"hazard identification/evaluation"; (2) develop methodologies—epidemiological, clinical (and clinical trials) and laboratory (such as positron emission tomography, nuclear magnetic resonance, etc.)—for the early detection—"exposure evaluation/risk characterization"—of these risk factors; and (3) discover modalities—biological, environmental, behavioral—to intercept or reduce risk—"risk management"—at the appropriate phase in the natural history of relevant chronic neurological and communicative diseases and disorders. Such intervention would be possible only after unraveling the underlying physiopathogenesis resulting from exposure to the risk involved. These disorders include stroke, Huntington's disease, multiple sclerosis, inborn errors of metabolism, disorders of hearing, epilepsy, post-traumatic epilepsy, cerebral palsy, Parkinson's disease, brain and spinal cord injury, Alzheimer's disease, AIDS, measles, amyotrophic lateral sclerosis, genital herpes, neurotoxicity, adverse diet-related nervous system effects, speech and language disabilities, muscular dystrophy, myasthenia gravis, and slow virus infection (Jacob-Creutzfeldt disease).

Division of Research Resources. The DRR strengthens and enhances the research environments of institutions engaged in health-related research by developing and supporting a wide variety of essential research resources. Because of the multidisciplinary nature of the division's programs, it contributes to the wide scope of hazard identification and characterization research supported by the Public Health Service (PHS). The division supports research to delineate high-risk groups that are predisposed to disease due to genetic, ethnic, behavioral, or environmental factors. Some studies are identifying etiologic factors that can be used to screen high-risk groups. Other studies are investigating (1) the risks of cancer associated with smoking or radiation exposure, of glaucoma associated with ocular hypertension, and of cardiovascular disease associated with culture, personality, diet, and genetics; (2) risk factors in Alzheimer's and multi-infarct dementia; (3) the risks of infectious disease in hospital employees and patients; (4) high-risk pregnancies and other factors leading to low birth weight, intrauterine growth retardation, Sudden Infant Death Syndrome (SIDS), and inborn errors of metabolism; (5) the risk of neural tube defects or hearing loss in premature infants; (6) the risks of depression and alcoholism related to personality development; and (7) biochemical risk factors in mental disorders. Dental clinic screening is attempting to identify patients at risk for osteoporosis.

Although most of the health risk assessment activities summarized are components of the hazard identification and hazard characterization steps of risk assessment, some of the activities aimed at identifying high-risk individuals and monitoring prevalence of diseases within a population are components of exposure characterization as well.

In general, risk determination activities are not part of NIH health risk assessment activities. However, each institute does administer public education and information dissemination programs that require an evaluation of the overall strength and validity of research results before conclusions or recommendations based on the research are communicated to health care providers and/or the public. When the topic under evaluation is the strength of the evidence supporting a particular agent's role as a causative agent for disease, this evaluation constitutes a risk determination. Such risk determinations may be accomplished through in-house reviews, scientific conferences, and workshops on various research topics. An example of this type of activity is the NIH Consensus Development Program.

Scientific Review

As mentioned earlier, intramural research projects are reviewed for scientific merit by each institute's board of scientific counselors. As part of this review, research results are also evaluated. Written reports of extramural research results are submitted to the appropriate program officer within the extramural research program for review. Both intramural and extramural scientists also submit research reports to peer-reviewed professional journals.

Each of the institutes also conducts reviews of research results as part of special workshops, conferences, etc., that are convened on various topics. Research results are reviewed as part of the Consensus Development Conferences that are jointly sponsored by one or more of the individual institutes and the NIH Office of Medical Applications of Research (OMAR).

Public Involvement

Priorities for each institute are influenced by public and congressional interest, as well as by advisory committees and boards that include public representatives. Some institutes, such as the NHLBI and the NCI, hold open meetings throughout the country to allow public comment on institute programs.

Description of Risk Assessment Reports

The NIH produces many publications that report the progress and results of its risk assessment activities. In general, these publications fall into two categories: those for scientists and health professionals and those for the general public. Professional publications are technical, scientific, and research-oriented; they are written primarily for biomedical researchers, physicians, and other health-related professionals. Other publications for health professionals are intended to provide up-to-date information so that they can provide better health care; they include reports of NIH research findings, conference and workshop proceedings, monographs, technical reports, and professional journals as well as such guides as NHLBI's "How to Help Your Hypertensive Patients Stop Smoking."

The pamphlets, booklets, fact sheets, and posters produced for the general public are primarily health education and promotion materials that provide broad information about diseases and disease conditions and what research is being done on them. Some focus on specific health problems, providing important facts for persons with or concerned about specific diseases, such as NCI's "What You Need to Know About Cancer of the Lung" for lung cancer patients. Others focus on promoting good health habits, such as NHLBI's "Exercise and Your Heart."

Mechanisms for Forwarding Results for Policy Decisions

Three types of policy decisions are influenced by the results of NIH health risk assessments: regulatory policy, research policy, and information/technology transfer policy. The NIH does not usually forward assessment results directly to any regulatory body. NIH-funded investigators must send the FDA reports of adverse effects of a treatment under investigation, but it is the individual investigator, not the NIH, who is required to submit this information. There are informal channels for communication of NIH research findings to regulatory agencies. For example, planning committees for Consensus Development Conferences that focus on issues of interest to the Food and Drug Administration (FDA) often include FDA representatives. Research results from the chemical testing program of the NIEHS are communicated to members of the executive committee of the National Toxicology Program (NTP), which includes directors of the FDA, the Environmental Protection Agency (EPA), the Consumer Product Safety Committee (CPSC), and the Occupational Safety and Health Administration (OSHA).

The second type of policy decision, the setting of research priorities, concerns the NIH more directly. The section on agenda setting describes mechanisms used to determine the research agendas of the various institutes. More formal methods for setting national biomedical research policy are also employed. The advisory committees and boards of each of the institutes consider priorities as they review research activities. NIH research policy is also set at annual program planning meetings between institute directors and the director of NIH.

A third type of policy influenced by the results of NIH research is information/technology transfer. Outside panels of experts are often convened by the institute to evaluate the strength of the data supporting a research conclusion that might be disseminated. For example, the NHLBI convened a working group—the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure—to evaluate data on high blood pressure and heart disease and to develop a report of its findings. In other cases, panels of intramural scientists review data to determine their strength and the appropriateness of their release to various audiences. The decision to disseminate most kinds of research information rests with the institute director after a "concept" approval by the office of the assistant secretary for health.

Procedures for Disseminating Findings to the Public

Dissemination plans for the various publications described above depend on the intended audience. The availability of publications aimed at scientists and health care practitioners is announced in appropriate professional journals and in institute newsletters, while publications for the general public may be distributed with the help of media campaigns or directly through retail stores.

Evaluation of Public Health Effects of Assessments

There are few formal mechanisms for evaluating the effects on public health of NIH health risk assessments, primarily because of the difficulty and expense of measuring public health outcomes and of determining the causes of apparent changes in health indicators. However, "end-point" analyses are conducted when they are feasible. Some NHLBI evaluation activities have focused on the impact of programs addressing heart disease risk factors. In particular, the NHLBI has supported surveys to determine whether and how the results of the CPPT have affected the behavior of the public and physicians. Conducting prerelease and postrelease surveys will enable the institute to estimate both changes in public diet and changes in physician's dietary recommendations following the release of the trial results.

Review of Recombinant DNA Research: RAC

Recombinant DNA, or gene splicing, was first developed in the early 1970s. The technique recombines pieces of genetic material (DNA) from virtually any source and introduces them into a living "host" cell. These host cells can then maintain the new genetic code and reproduce it in daughter cells. In responding to concerns about possible hazards from genetically engineered lifeforms, the NIH established a Recombinant DNA Advisory Committee (RAC) to assess potential risks of recombinant DNA technology.

The RAC was given two fundamental responsibilities: (1) to develop and revise guidelines to set biological and physical containment standards for recombinant DNA experiments, and (2) to review individual applications for experiments not adequately addressed by the generic structure of the guidelines.

NIH Guidelines for Research Involving Recombinant DNA Molecules was published in 1976 and has been revised as necessary. The RAC review of individual applications is an ongoing process. RAC review is required only for institutions that receive NIH funds for recombinant DNA research. Private companies involved in recombinant DNA research undergo review and comply with RAC recommendations voluntarily. All RAC decisions regarding either revisions in the guidelines or proposed experimental protocols are submitted as recommendations to the director of the NIH, who makes the final policy decisions.

Mandate

The RAC was established in 1974 by the NIH in response to a recommendation from a National Academy of Sciences (NAS) committee that an advisory committee be established for "devising guidelines to be followed by investigators working with potentially hazardous recombinant molecules." Statutory authority was granted under 42 U.S.C. 217a, Section 222 of the Public Health Service Act, as amended. The RAC advises the Secretary of the Department of Health and Human Services (DHHS), the Assistant Secretary for Health, and the director of the NIH on the current state of knowledge and technology regarding DNA recombinants and recommends guidelines to be followed by investigators working with recombinant DNA.

Organizational Placement

Administrative support for the RAC is provided by the National Institute of Allergy and Infectious Diseases (NIAID) and consists of staff members within the Office of Recombinant DNA Activities (ORDA). The committee is composed of 25 members who are appointed by the Secretary or a designee. The chair of the committee is designated by the Secretary. Members serve overlapping terms of four years and are selected on the following basis:

- At least 14 members are persons knowledgeable in the fields of molecular biology or recombinant DNA research, or in scientific fields other than the above.
- At least six members are persons knowledgeable in applicable law, standards of professional conduct and practice, public attitudes, the environment, public health, and related fields.

Nonvoting liaison representatives of federal agencies are also included on the committee. Representatives of the Centers for Disease Control (CDC), the National Institute for Occupational Safety and Health (NIOSH), the EPA, the FDA, the Department of Agriculture (USDA), the Department of Defense (DOD), and the Department of State generally attend. Other nonvoting agencies are the Department of Commerce, the Department of Energy, the Department of Interior, the Department of Justice, the Department of Transportation, the Department of Labor, the Veterans' Administration (VA), the National Aeronautics and Space Administration (NASA), the National Science Foundation (NSF), the executive office of the President, the Nuclear Regulatory Commission, and the U.S. Arms Control and Disarmament Agency.

Agenda Setting

The agenda for each RAC meeting is set by NIH staff in consultation with the RAC chair. NIH staff receive and evaluate requests for RAC review of research projects as well as proposals to amend the guidelines. Anyone may submit either type of request. There has been no need for a priority-setting mechanism, because to date virtually all requests have been reviewed at the RAC meeting following their submission.

Risk Assessment Methods

The *NIH Guidelines for Research Involving Recombinant DNA Molecules*, issued by the NIH in June 1976, is the primary means by which biological and physical containment standards are established. These safety standards are based on an assessment of perceived risks posed by a recombinant DNA organism.

Certain experiments are exempt from the guidelines requirements. For other experiments, the guidelines specify a physical and biological containment level in which the experiment must be conducted. The RAC has estimated that about 95 percent of recombinant DNA experiments are covered by the generic guidelines. Different levels of containment appropriate for different recombinants are established by applying various combinations of the physical and biological containment levels. Physical containment levels are defined by the laboratory facilities and procedures required and range from P1 (the least stringent) to P4 (maximum containment).

There are also biological containment levels, which may require the use of disabled host-vectors for cloning and propagating organisms containing recombinant DNA. The objectives of biological containment are to minimize survival of the host organism outside of the laboratory and to minimize transfer of the recombinant DNA from the laboratory host to nonlaboratory hosts. Biological containment levels are designated HV1 (lowest) or HV2 (high level of biological containment); approximately 24 HV2 systems have been certified by the NIH.

The guidelines are administered primarily by principal investigators (PIs) and Institutional Biosafety Committees (IBCs), which the guidelines require at each institution (university, medical school, etc.) where recombinant DNA research takes place. Among the responsibilities of the IBCs is the review of certain experiments for compliance with the guidelines, and an independent assessment of what containment levels will be required or whether RAC review is necessary as specified by the guidelines.

The guidelines identify four situations that require special RAC review and specific NIH approval:

- Deliberate formation of recombinant DNA containing genes for the biosynthesis of certain molecules that are highly toxic to vertebrates;
- Deliberate release of a recombinant DNA organism (except certain plants) into the environment;
- Deliberate transfer of a drug-resistance trait to microorganisms that are not known to acquire it naturally; and
- Protocols involving human gene threapy.

RAC review is also required when the guidelines do not explicitly consider certain proposed recombinant experiments, or when researchers request a change in the containment level specified by the guidelines or the RAC, as in the cloning of the Shiga-like toxin, discussed later in the chapter. The determination that a particular experiment requires RAC review is the hazard identification step of the RAC assessment process.

If RAC review is required, the researcher must submit a protocol for the proposed experiment and any supporting evidence to the Office of Recombinant DNA Activities. The RAC reviews the evidence presented by the researcher and any pertinent outside literature, as the hazard characterization step of the assessment process.

In the exposure characterization step for laboratory research, RAC has considered the following types of concerns:

- Unintended dispersal of the organism into the environment, such as the swallowing of genetically altered bacteria by an investigator using improper techniques.
- Survival of the organism in the environment, or transfer of the recombinant molecule into another organism, such as survival in the gut of an investigator or in sewage, or the transfer of an antibiotic resistant vector from experimental bacteria to bacteria occurring naturally in the gut of an investigator.
- Acquisition of a selective advantage by the recombinant-containing organism that would allow it to populate a significant ecological niche, such as the acquisition of antibiotic resistance enabling bacteria to reside in the gut.
- Change in the natural biology of the organism so that it becomes a danger to some higher organism, such as the acquisition by a toxin-producing bacterium of the ability to bind with the epithelium of the gut, thus giving it virulent characteristics.

It is sometimes possible to make a quantitative exposure characterization, such as the likelihood that a certain quantity of bacteria will spread a certain distance from a laboratory of a given containment level, or how long a given strain of bacteria may survive in sewage. However, because recombinant DNA research is a new and rapidly expanding field, the data necessary for making firm quantitative evaluations are generally unavailable. Thus, the RAC generally makes qualitative assessments based on the most recent available data, but—perhaps because of the effectiveness of the RAC itself—is virtually always dealing with risks that have not resulted in demonstrable harm to human health.

In the risk determination step of the assessment, the RAC analyzes the adequacy of the available data and weighs the risks involved. After thorough discussion, a vote is taken to approve, deny, or require further information to support the request. This vote determines the recommendation to be submitted to the director of the NIH.

The early guidelines, which were developed before the possibility of harm based on these criteria could be properly evaluated, presumed that all recombinants presented some level of potential risk. More recent versions of the guidelines reflect current opinion that concern should be limited to organisms capable of establishing themselves in the environment and possessing potentially harmful properties. As new evidence becomes available, the guidelines are revised to exempt or permit lower containment levels for certain classes of experiments that present no substantial risk to health or the environment.

Scientific Review

In general, the decisions made by the RAC constitute formal peer review but two mechanisms have been established to provide broader scientific review of those few assessments that require scientific expertise not available from the RAC. The first is the establishment of multidisciplinary working groups of the RAC and non-RAC members with expertise in a specific topic under consideration. For example, the Working Group on Release into the Environment was established to assess the risks of releasing recombinant DNA organisms into the environment. Once a working group reviews the topic or experiment under consideration, a recommendation is made to the RAC, which in turn reviews the information and makes a final recommendation to the NIH director.

The second mechanism for enhancing scientific expertise is to use ad hoc consultants when there are gaps in scientific knowledge or expertise within the RAC, but a working group is not necessary.

Public Involvement

A proposal to modify any section or to introduce new provisions into the guidelines must be published for public and professional comment in the *Federal Register* at least 30 days prior to an RAC meeting. Under Public Law 92-463, all sessions of the RAC are announced in advance in the *Federal Register*, and most are open to the public.

Description of Risk Assessment Reports

Following each RAC meeting, the ORDA issues minutes and makes them available to any interested party. These reports are detailed accounts of meetings, including any comments and assessments made on setting containment levels for an experiment undergoing review. The RAC also submits a comprehensive annual report to the secretary of DHHS, the assistant secretary for health, and the director of the NIH containing: (1) information on the functions of the RAC; (2) a list of members and their business addresses; (3) the dates and places of meetings; and (4) summaries of the committee's activities and recommendations during the fiscal year.

Mechanisms for Forwarding Results for Policy Decisions

The director of the NIH is responsible for policy decisions on recombinant DNA technology. The RAC functions as an advisor, assessing both the necessity for guideline revisions, which are based on submitted proposals that point out new safety or risk considerations, and the safety of individual experiments. Risk assessments and recommendations made by the RAC are forwarded to the director of the NIH via an oral briefing by the executive secretary of the RAC.

Approximately 10 to 15 percent of the RAC recommendations are not approved by the director, almost always because of an apparent lack of RAC consensus reflected in the voting. In general, if two or more RAC members vote against the majority, the NIH director will request information concerning the lack of consensus, either during the oral briefing, if the dissenting members were clear in stating their reasons for voting against the proposal, or through the ORDA if the reasons were not clear. Based on this information, the director makes a decision. If a proposal is denied, the ORDA sends a letter to the investigator stating the reasons.

The investigator may reapply for review of the proposal or submit a modified proposal.

The director may refer a RAC recommendation back to the committee for clarification. In this case, the director appends a list of questions about the proposed action and requests reconsideration.

Procedures for Disseminating Findings to the Public

Major actions taken by the NIH on RAC recommendations are published in the *Federal Register*, enabling other persons, organizations, and agencies to gain access to relevant new risk assessment information. Policy-related questions resulting from information contained in the *Federal Register* are directed to the ORDA for consideration.

Information is also disseminated via the *Recombinant DNA Technical Bulletin*. This quarterly publication is sent directly to the chairs of all IBCs registered with the ORDA, to principal investigators of NIH grants and contracts involving recombinant DNA, to the chairs of advisory committees in other countries, and to other interested groups or individuals who request the bulletin from the ORDA. The bulletin links investigators involved in recombinant DNA research with other people and organizations active in this area and reports recent scientific progress in many areas of recombinant DNA research.

Evaluation of Public Health Effects of Assessments

The RAC does some follow-up, especially where new areas of research have been approved. This follow-up is basically of a "strings-attached" nature. The RAC may require, as a condition for approval of an experiment, that the investigator perform certain monitoring experiments that are designed to assess possible adverse effects of the main experiment. The monitoring data are sent to the RAC, which can then report any problems to the director of the NIH for immediate action.

Consensus Development Conferences: OMAR

The Consensus Development Program at the NIH brings together biomedical research scientists, practicing physicians, consumers, and others in an open forum, termed a consensus development conference, to assess publicly the value of one or more medical technologies and to reach general agreement on their safety and efficacy. The technology being assessed may be a device (e.g., blood-pressure measuring instrument), a drug (e.g., postmenopausal estrogen), a medical, surgical, or dental procedure (e.g., Cesarean childbirth) or a lifestyle change. Conferences have addressed such topics as breast cancer screening, coronary artery bypass surgery, and liver transplantation. Some conferences examine more than a single technology, such as a broad health problem (e.g., "Travelers' Diarrhea") and various means of dealing with it.

The consensus development process for a technology uses assessments of the risks and benefits of a technology to formulate recommendations to practicing physicians and the public regarding its use. Thus, all four steps of risk assessment as well as risk management are essential facets of the program's larger role in health technology assessment and transfer. As of April 1, 1985, 49 conferences had been held.

Mandate

The Consensus Development Program was initiated in 1977 by the director of the NIH. The program has two primary objectives: (1) to evaluate in a public setting the clinical utility of a health care technology and (2) to foster the dissemination of information on advances in biomedical technology to consumers and physicians.

Organizational Placement

The Consensus Development Program is a major activity of the Office of Medical Applications for Research (OMAR) within the office of the director of the NIH. The OMAR office is headed by the associate director for medical applications of research.

Agenda Setting

The OMAR requires that each topic selected for a consensus development conference meet these five criteria:

- The subject must be medically important.
- There must be a scientific controversy that would be clarified or a gap between current knowledge and practice that could be narrowed by the consensus approach.
- The topic must have an adequately defined and available base of scientific information.

- The topic must be amenable to clarification on scientific grounds and the outcome should not depend mainly on impressions or value judgments.
- The timing of the conference must be such that it is likely to have a meaningful impact.

The following qualities are also desirable: public health importance, health care cost impact, preventive impact, and public interest.

An agenda is developed informally each year for conferences beginning approximately 14 to 16 months later. Topics may be suggested by the 14 NIH BIDS, the OMAR, other government health agencies, and the public. A topic is selected when there is agreement between a sponsoring BID and the OMAR. For the purposes of this program, the National Institute of Mental Health (NIMH), a component of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), is treated as if it were an NIH BID. Final approval of each topic rests with the director of the NIH.

About eight conferences are held each year. The number of topics suggested and sponsored by the BIDs has never exceeded the number that could be supported with available resources, so there has been no need to set priorities among the topics nominated by the BIDs.

Risk Assessment Methods

The OMAR has developed the following basic principles for planning and conducting consensus development conferences:

- An independent, broad-based panel is assembled for each conference in order to give balance, objectivity, and knowledgeable attention to the topic.
- The panel meets in public session for the presentation of all data, commentary, and discussion.
- The principal role of the panel is to develop responses to several specific questions that determine the scope and direction of the conference. These questions are developed and widely circulated in advance.
- At the close of the conference, a draft consensus statement is prepared by the panel in executive session and is presented to the conference in plenary session. Following public discussion, the panel returns to executive session and adopts a final consensus statement that stands as the record of the conference.

- Wide dissemination of the consensus statement is effected to achieve maximum impact on health care practice.

This process is described in detail in "Guidelines for the Selection and Management of Consensus Development Conferences," which is available from the OMAR.

The hazard identification and hazard characterization steps of risk assessment enter the consensus development process through the review of pertinent data on the safety and risks of a treatment or medical technology. Data may come from a variety of studies, including microbial, animal, and human studies. Only previously published data are considered; no original research is undertaken. For hazard characterization (i.e., determining the strength of the association between criteria adverse effects and the medical technology under consideration), controlled clinical trials are the most useful methodology, but data from epidemiologic investigations, animal studies, and other kinds of clinical reports are also considered. Exposure characterization most often focuses on the prevalence of the disease, with special attention to any subpopulations that may be at increased risk of adverse effects of the disease and/or treatment. The conclusions of the consensus panel constitute the risk determination step of the process. These conclusions are framed as recommendations to practicing physicians and, less often, to the lay public. The panel's determinations of risk are sometimes expressed in qualitative rather than quantitative terms.

The NIH staff who attend the executive sessions where the recommendations are formulated have described the decision process as an essentially open scientific discussion where differing views are examined. The NIH staff encourages the panel to include differing views in the consensus statement rather than to develop a less comprehensive statement that the full panel would endorse. Minority statements may be included, but have rarely been necessary.

Key aspects of the consensus development process that affect the risk determinations made by the panel are: (1) framing the questions to be addressed; (2) selecting consensus panel members; (3) selecting conference speakers (i.e., selecting data to be considered); and (4) developing the consensus statement.

Framing the Questions. Generally, four to six questions are developed prior to the conference by a planning committee composed of NIH staff and outside experts who are selected ad hoc for each conference by the sponsoring BID in consultation with the OMAR. The questions usually concern the basic scientific information pertinent to the topic, the efficacy of the technology, the safety of the technology, clinical applications, any public health issues specific to the topic, and future research needs.

Selecting a Consensus Panel. A panel of about 12 persons is nominated by the planning committee. The guidelines developed by the OMAR for consensus conferences specify that four types of individuals be included on the panel: research investigators in a field relevant to the topic; health care professionals who use the technology; methodological specialists—epidemiologists and/or biostatisticians; and nonscientist members of the public with relevant knowledge, such as lawyers, ethicists, and patients. There are at least two representatives from each group, but research investigators usually form the largest group. To minimize bias, persons who have taken public positions concerning the topic are not selected for the panel. The selection of federal employees is prohibited.

Selecting Conference Speakers. Selection of consensus speakers determines the data to be examined and evaluated at the conference. Speakers are generally basic scientists or clinicians who are selected for their scientific expertise. Where scientific controversy exists, speakers are chosen so that all major views are presented. Interested individuals and organizations are encouraged to present their views as well.

Developing Consensus. The consensus development process per se requires that the panel be familiar with the underlying scientific information on safety/risk, listen to oral presentations of risk-related data, and develop a consensus on the risks. Because the panel is asked also to consider the efficacy (i.e., benefits) of the technology and to make public health recommendations, certain aspects of *risk management* are included in the consensus development process.

The recommendations of the consensus statement are those of the panel and are not NIH policy statements. The statement has no legal or regulatory status, and the practicing physician or the public can choose to follow or ignore its recommendations.

Scientific Review

No formal external peer review of a consensus statement is incorporated into the consensus development process because the process itself is an exercise in peer review, and the conferences are generally organized to emphasize the scientific review of the technical information available on a subject. When the draft consensus statement is read at the final session of the conference, conference participants are invited to comment. At the discretion of the panel, the comments are often incorporated into the statement.

Public Involvement

The consensus development process includes three channels for public involvement:

- Public representatives are included on the consensus panel.
- Meetings are open and widely publicized, and public comments are encouraged throughout the conference.
- The public may comment on the draft consensus statement.

Description of Risk Assessment Reports

The consensus statement issued at the close of a conference includes the panel's answers to each of the questions posed prior to the conference, which usually include some element of risk assessment. Consensus statements generally discuss the significant issues and provide information on efficacy and safety, and recommended use of the technology. However, the statements are relatively brief, and are directed to clinicians and the lay public. They usually indicate the data upon which they are based, but do not provide detailed analyses of that data.

Mechanisms for Forwarding Results for Policy Decisions

It is usually not necessary to forward a consensus statement to other government bodies because the statement centers on recommendations to practicing physicians. Nonetheless, other government agencies are made aware of consensus conferences through the participation of OMAR staff in two broad intergovernmental committees: the Coordinating Committee on Assessment and Transfer of Technology (CCATT) and the Technology Coordinating Committee (TCC). The CCATT, which closely observes the Consensus Development Program, is an NIH-wide committee whose meetings are attended by representatives of PHS organizations. The TCC is a PHS committee whose meetings are attended by representatives of several other federal agencies and organizations outside the government.

In a few instances, panels have made recommendations that indirectly relate to the legislative process or the function of agencies other than the NIH. An example is the consensus statement of the conference on "Lowering Blood Cholesterol to Prevent Heart Disease," where the panel recommended that food labeling should include specified information relating to cholesterol, fat content, and calories in order to facilitate dietary control of blood cholesterol. However, there were no references to any agency or to the rule-making process. Since the consensus statement presents the opinion of the panel rather than NIH policy, such references would be strongly discouraged by NIH staff, who are always present during the drafting of the statements.

Procedures for Disseminating the Findings to the Public

The results of Consensus Development Conferences are disseminated to practicing physicians and others in the health care system, the biomedical research community, and the public. Almost all consensus statements have been published in the *Journal of the American Medical Association (JAMA)* and in specialty journals pertaining to the topic. Within three months after each conference, printed copies of each consensus statement are mailed to some 20,000 individuals and organizations with relevant interests. Copies of the consensus statements are available from the OMAR upon request.

Evaluation of Public Health Effects of Assessments

There is no formal mechanism for monitoring the impact of consensus statements on regulatory decisions or other policy decisions of the federal government. The OMAR has sponsored a survey conducted by the Rand Corporation that asked, among other things, whether physicians in specialties related to a conference had heard of the recommendation of the conference panel. About 40 percent reported awareness of the recommendation. Another portion of this study, not yet completed, will examine the extent and means by which the results of the Consensus Development Conferences are being communicated and used.

Protection of Human Subjects of Research: OPRR

Widely accepted ethical standards require that risks to human subjects of biomedical and behavioral research be justified by the anticipated benefits to the subjects or to society. This principle is incorporated in the Regulations for the Protection of Human

Subjects of the DHHS codified at 45 CFR 46. The Office for Protection from Research Risks (OPRR) of the NIH has been delegated responsibility for ensuring that research involving human subjects is conducted in accordance with the regulations and contains adequate safeguards for subjects.

The regulations mandate the establishment of Institutional Review Boards (IRBs) located at approximately 3,000 to 5,000 research organizations to assess, among other considerations, the risks and benefits of proposed research. The OPRR provides general guidance to the IRBs on the interpretation and application of the regulations and on questions of research risks. The IRBs approve or disapprove proposed research at or sponsored by their institution, in large part on the basis of their assessment of risks and benefits.

Each grant application or contract proposal that is supported by the NIH and involves human subjects must be covered by an "assurance of compliance" negotiated with the OPRR before an award can be made. The DHHS will fund only those research activities that are covered by such an assurance and for which the institution has certified IRB approval that the risks are acceptable. The assurance states that the institution will comply with the requirements set forth in the Code of Federal Regulations to protect human subjects against the risks entailed in the research.

Mandate

The OPRR was delegated departmentwide responsibility in 1974 by the DHHS to implement the newly promulgated regulations for the protection of human subjects. Statutory authority was granted under Section 474 of the Public Health Service Act and implemented by regulations (45 CFR 46, as amended).

Organizational Placement and Staff

The office of the director of the NIH provides administrative support for the OPRR. Each IRB is located at an institution where research is carried out and receives its administrative support from the institution. IRB members are appointed by the administration of the institution, with approval by the OPRR. The regulations require that the IRB be constituted so as to ensure complete and adequate review of research activities commonly conducted by the institution. The IRB members must be qualified through experience and expertise, and possess professional competence to review specific research activities. At a minimum, the IRB must have:

- Five members;
- Both male and female members;
- At least one nonscientific member (e.g. lawyer, ethicist, clergy); and
- At least one member having no affiliation with the institution other than IRB membership and no immediate family member affiliated with the institution.

IRBs must review research at convened meetings with a simple majority quorum, which must include the nonscientific member.

Agenda Setting

IRBs must review all research activities involving human subjects that are not specifically exempted by the regulations. (The exemptions defined in the regulations designate certain types of research with no or little risk.) The IRB may determine that some activities be reviewed more frequently than annually if the degree of risk posed by the research procedure warrants more frequent review.

Prior to award, the OPRR reviews all grant applications and contract proposals that are shown to require resolutions of concerns that risks to subjects are, or appear to be, at an unacceptable level. In accordance with the statutory mandate, the OPRR conducts a program of education and guidance on risk/benefit issues in biomedical and behavioral research involving human subjects. The program is aimed at investigators, administrators, and IRB members at the 3,000 to 5,000 institutions where research covered by the regulations is conducted.

Risk Assessment Methods

A grant application or contract proposal to be submitted to the DHHS is first reviewed by the applying institution's IRB. The IRB determines whether the risks of the proposed research are acceptable in relation to the benefits to the subject and others and the importance of the knowledge to be obtained. The IRB is required to:

- Review all research activities covered by regulations, and to approve, require modification in, or disapprove the research.
- Determine that information to be given to subjects as part of informed consent is in accordance with the regulations, and to require additional information if it would add to the protection of the rights and welfare of the subjects.
- Determine how the informed consent is to be documented.

- Notify investigators and the institution in writing of its decision to approve or disapprove a proposal.
- Continue to review research at intervals appropriate to the degree of risk, but not less than once per year.
- Report to the OPRR unanticipated problems involving risks to the subjects or to others.

The IRBs must assess the risks and anticipated benefits of proposed research according to criteria stipulated in the DHHS regulations. The criteria are elaborated below:

1. *The risks to subjects are minimized to the extent possible.* "Risk" is defined as the "probability and magnitude of possible harm or injury—physical, psychological, social, or economic." The IRB must first identify the risks associated with the research and then determine that the risks are minimized. In making this determination the IRB must consider whether the procedures used are consistent with sound research design and carry no unnecessary risks. The IRB must also determine that, whenever appropriate, the procedures are those already being performed on the subjects for diagnostic or treatment purposes. The IRB is directed to differentiate the risks of research proper from risks the subject would undergo in the course of accepted practice for treatment or diagnosis.

Unnecessary risks are to be avoided at all times. The IRBs must assure that the research design includes adequate safeguards to reduce or manage risks that are unavoidable (e.g., frequent monitoring of subjects, or coding of data to ensure confidentiality). Precautions, safeguards, and alternatives can be added to the research design to reduce the probability and/or severity of harm.

2. *The risks are reasonable in relation to anticipated benefits, if any, to subjects, and to the importance of the knowledge to be obtained.* The IRB must identify the probable benefits, if any, to the subjects or to society. A "benefit" of research may be understood as the acquisition of knowledge that may eventually lead to improved understanding of normal or disease states of human beings and thus result in improved medical care, health status, or quality of life. The benefits of research may also directly result in an improvement of the health or well-being of individuals who take part in the research. However, the purpose of research is to obtain new knowledge and the IRB must consider the importance of the knowledge in determining the reasonableness of the risks, particularly when the research is not expected to benefit subjects directly.

The major judgment that the IRBs must make is the evaluation of risks versus benefits. The risk/benefit assessment is not technical and quantitative, but is a judgment based on available information provided in the research protocol regarding the hypothesis under question. Laboratory and animal studies, literature references, professional and clinical experience, and any data that may exist are to be used in making the assessment. It is inherent in research that results and risks are not entirely known in advance, but reasonable approximations are possible and the IRB relies on them in making its judgments.

Each research proposal must be reviewed on its own merits, and different IRBs may come to different risk/benefit assessments of a particular protocol. IRB decisions depend on current information on the risks and benefits and the reliability of this information.

The proposed subjects of the research must be considered in assessing risks because the degree of risk may vary across classes of individuals. Specific protections are mandated for special groups (e.g., children, pregnant women, and persons who are seriously ill, chronically or acutely). The setting of the research may be evaluated as well. Risks acceptable in a clinical research unit, for example, differ from those in field settings.

3. *The research subjects are provided with a description of risks and benefits*. Even though this is not technically part of the assessment process, the consent process must include a delineation of the probable risks and benefits to enable a research subject to determine his/her willingness to participate in a particular study.

4. *Intervals for periodic IRB review and the need for other monitoring are determined*. The IRB is asked to determine how often the IRB should review the research project and whether an independent Data and Safety Monitoring Committee is necessary to oversee large studies and to keep the IRB informed of significant new findings. DHHS regulations require reevaluation of research projects at intervals appropriate to the degree of risk, but at least once a year. Periodic reviews are necessary to determine whether the risk/benefit assessment has changed because of unforeseen risks or benefits, or for other reasons. The IRB may need to reassess the research project and may require modification or termination of the activity. Between reviews, the researchers are required to inform the IRB of information that would affect the risk/benefit assessment.

Scientific Review

Grant and cooperative agreement applications (individual research grants, center grants, program project grants) with IRB approval are sent by the institution to the NIH. The application is assigned to a scientific study section composed of approximately 12 scientists, usually nonfederal, who review the application and evaluate not only the scientific merit of the proposal but also the types of risks and the adequacy of safeguards. The study section prepares a summary report with one of the following recommendations: (1) the application be approved for funding with a priority assigned; (2) the application be approved for funding with an assigned priority, but coded to indicate that the reviewers were concerned that a serious risk exists; or (3) the application be disapproved for funding. If an application is coded to indicate possible serious risks to human subjects, the institution and investigators are notified. If possible serious risks are identified, the application cannot be funded until the concerns are resolved to the satisfaction of the NIH. Scientific review groups may disapprove applications that present unacceptable risks.

Contract proposals must receive IRB approval before submission to the appropriate technical merit review panel by a similar process.

Public Involvement

Each IRB has at least one nonscientific member who must be present at all reviews of research involving human subjects. In addition, the summary reports from the scientific study sections must be reviewed by the appropriate national advisory board or council, which has members chosen by the director of the NIH and approved by the secretary for the DHHS, including public or lay representatives. The national advisory board or council may concur with the recommendations of the scientific study sections, or disapprove a given recommendation for support, but it may not approve for support an application that has been disapproved by the scientific study section.

Description of Risk Assessment Reports

The application to the DHHS is accompanied by an Assurance/Certification/Declaration form (DHHS 596), which provides preliminary information for the NIH and the scientific review body relative to the status of IRB review and assurance of compliance by the applicant institution.

Following merit review, the scientific review body prepares an administrative summary for each reviewed application that summarizes the recommendations and the priority set for the project.

The summary statement also indicates an evaluation of risks to human subjects. In the case of contract proposals a similar summary is proposed.

Mechanisms for Forwarding Results for Policy Decisions

The IRB records its recommendations on DHHS form 596, which accompanies the application or proposal to the NIH. The scientific review body formulates a recommendation that is sent to the appropriate program and then, in the case of grant applications, to the appropriate national advisory board or council, which may then approve the application. Final approval of all applications and proposals is made by the director of the NIH as delegated by the secretary of DHHS.

Procedures for Disseminating the Findings to the Public

IRB risk assessment findings are not disseminated to the public.

Evaluation of Public Health Effects of Assessments

While the IRB is mandated to make at least annual reviews of each approved research project, either the IRB or the study section can require that reviews be performed more often when the possibility of serious risk exists. All adverse effects must be reported by the institution to the NIH, and if the research is regulated by the FDA, the FDA must be notified as well.

CASE STUDIES

Dietary Fat and Cancer: NCI

Several publications of the National Cancer Institute (NCI) provide dietary guidelines intended to reduce the risks of cancer. These guidelines are based on a risk assessment developed under contract from the NCI by a Committee of the National Research Council (NRC) of the NAS. The most recent NCI publication is "Diet, Nutrition and Cancer Prevention: A Guide to Food Choices."

The NRC assessment makes a qualitative determination of the effect of diet and nutrition on cancer incidence. In order to make this assessment, the committee reviewed extensive data on dietary components (including fats, protein, carbohydrates, fiber, vitamins, minerals, environmental contaminants, additives, and alcohol) and their relation to cancer. The committee reached its strongest conclusions on the association between dietary fats, with some relation to fiber, and the risks of cancer.

Hazard Identification

A large number of epidemiologic studies have indicated that the incidence of common cancers in humans is determined by potentially controllable, external factors, in that the kinds of cancer that affect people in different parts of the world depend on their habits, diets, and customs more than on their ethnic origins. For example, some studies have indicated that the age-specific incidence and mortality rates of many of the common nonrespiratory cancers are higher in certain nonindustrialized nations, such as New Zealand, than in the United States. Thus, it seemed likely to the committee that the initiators and promoters of common cancer are, for the most part, related less to industrialization than to various other long-standing behaviors, especially diet and smoking.

Hazard Characterization

Studies have indicated that both saturated and unsaturated fats are associated with the occurrence of cancers in laboratory animals:

- When the percentage of calories derived from fat increases, the risk of certain cancers increases.
- In rats and mice fed a diet low in total fat, polyunsaturated fats are more effective than saturated fats in enhancing tumorigenesis; data on humans do not permit a clear distinction between effects of different components of fat.
- Dietary fat promotes tumorigenesis in mice; when dietary fat is increased, the incidence of skin tumors occurring after exposure to coal tar increases. Similar results hold for mice treated topically with 3-methylcholanthrene.
- High-fat diets enhance breast tumorigenesis in both rats and mice exposed to tumor initiators. At low doses of initiating carcinogens, high fat intake appeared to decrease the latent period and increase mammary tumor incidence. At high doses of initiators, high-fat diets increased the incidence and numbers of mammary tumors but had no effect on latency. These

results are consistent with the theory that dietary fat exerts a promoting, rather than an initiating, effect on tumorigenesis.
- In mice and rats, increased lipid intake is associated with enhanced growth of transplanted adenocarcinomas as well as increased incidence of carcinogen-induced hepatomas. Increasing the quantity of dietary fat increases the incidence and yield of bowel tumors induced by a variety of carcinogens.

After reviewing more than 20 experimental studies (almost all in rats) of the influence of dietary fats on carcinogenesis, the committee concluded that dietary fat content clearly affects tumor incidence in the breast, colon, liver, and pancreas.

Over 30 epidemiological studies of the associations between dietary fat and cancer have indicated that the strongest association is seen for cancers of the large bowel. Some associations have been observed for other gastrointestinal organs, and such endocrine target organs as the breast, endometrium, and prostate.

- Several international correlation studies have shown a direct association between per capita total fat intake and colon cancer incidence and/or mortality.
- A case-control study in Canada showed a direct association between the risk of colon and rectal cancer and the consumption of fat, especially saturated fat.
- A group of colon cancer patients in Israel had higher fat and lower dietary fiber intake than a control group.
- A case-control study of colon cancer in black patients in California revealed a direct association between risk of colon cancer and frequent consumption of high-fat, especially saturated fat, foods. The association was strongest for those with a high-fat, low-fiber diet.
- Studies designed specifically to test the hypothesis that fat consumption is associated with colon cancer tend to show striking associations, especially when the possible confounding effects of dietary fiber are considered.
- Several international correlation studies have shown a direct association between per capita fat intake and breast cancer incidence or mortality.
- A case-control study of breast cancer in Canada estimated that 27 percent of the risk of breast cancer for women was attributable to total dietary fat intake.
- Several international correlation studies plus one Japanese and one American study reported a strong correlation between per capita fat intake and mortality due to prostate cancer.
- A study in Hawaii showed that the incidence of prostate cancer

was highly correlated with consumption of both animal and saturated fat in four ethnic groups.

- Two case-control studies showed that patients with prostate cancer had consumed high-fat foods with greater frequency than matched hospital control subjects.

However, it is not possible to draw definitive conclusions from these studies because other well-designed studies have not demonstrated these associations.

Exposure Characterization

Although it has been estimated that Americans derive 40 percent of their calories from fat, no other estimates of exposure to dietary fats have been developed and no direct measures of exposure to dietary fat have been developed other than nutritional assessment by interview. However, various biochemical methods involving feces analysis are now under investigation.

Risk Determination

The qualitative assessment of the association between diet and/or nutrition and the risks of cancer, and the recommendations, were based on the overall strength of the evidence; the committee did not emphasize the results of any single study. Epidemiological methods for determining dietary risk factors associated with cancer were examined in descriptive, correlation, case-control, and cohort studies. Greatest confidence was placed in the results of case-control and cohort studies, in which the investigators could control for confounding variables. The committee found the results of these studies more definitive and indicative of meaningful associations than the descriptive data presented in other kinds of observational studies.

The committee stated that the focus of epidemiological studies on human populations circumvents two important limitations of laboratory research. First, the results do not have to be extrapolated from experimental animals to humans. Second, extrapolation from high to low doses is avoided because levels and patterns of exposure studied are those that actually occur among human populations. The relation between "dose" and response may be observed directly. However, applicability of the results of epidemiological studies is limited by several difficulties. In the first place, observational studies are open to errors or bias. Choice of nonrepresentative subjects, such as hospitalized patients, for example, may yield misleading results. Second, the determination of exposure to specific dietary constituents is difficult, and the delay in overt manifestation of illness makes correlation of dietary factors with disease onset difficult to establish. Third, the interpretation of epidemiological studies is greatly complicated by the heterogeneity of human populations, and by the wide variety of changing lifestyles. Finally, the biggest problem noted by the committee is the difficulty of determining accurate measures of exposure variables from recall data obtained by interview. The greatest weakness in epidemiological studies is the absence of quantitative data on exposures.

Results from epidemiological studies were supplemented with laboratory evidence in the NRC's qualitative assessment. The committee placed greatest confidence in data derived from studies involving more than one animal species or test system, on results that were obtained in more than one laboratory, and on data that indicated a direct relationship between dose and response. At the same time, the committee recognized that the extrapolation of effects from animals to humans is difficult and uncertain at best, and that both qualitative and quantitative differences in the effects of diet on humans and laboratory animals may complicate the task of drawing inferences about human risks.

The committee concluded that, of all dietary components studied, fat intake is most strongly associated with increased cancer incidence. In general, specific components of fat have not been clearly identified as responsible for certain cancer incidences in humans, although total fat and saturated fat have been implicated most frequently. The risk is greatest for colon, prostate, endometrial, and breast cancers. However, it is not generally possible to clearly attribute increased risks of cancers of various sites to fat intake because dietary fat is highly correlated with the consumption of other food constituents (especially protein in Western diets, and perhaps low fiber). Based on these findings, the committee recommended that saturated and unsaturated fats be reduced in the average U.S. diet from approximately 40 to 30 percent of total calories. It was noted that the data could be used to justify an even greater reduction, but that this 25 percent reduction represents a moderate and practical target, and is likely to be beneficial.

The NCI continues to review research results concerning the relation between diet and cancer. Since the NRC review, several studies have been designed to resolve unanswered questions. For example, due to the reciprocal relationship between dietary fat and dietary fiber (diets high in fat are usually low in fiber and vice versa), the committee was unable to determine their independent effects. New studies focusing on this issue sought populations that were similar in one of these respects and different in the other. One epidemiologic study compared the cancer risks of two Finnish populations both having high fat intakes, but differing fiber intakes. Analysis showed that dietary fat and dietary fiber are independently related to cancer risk.

The NCI also supports case-control and cohort investigations designed to elucidate aspects of the diet-cancer relation that have not yet been resolved. One controlled clinical trial currently being initiated by the NCI will investigate the relation between dietary fat intake and breast cancer in women. Approximately 10,000 women already at high risk for breast cancer will be randomly assigned to their usual diet or a diet in which only 20 percent of the calories are fat; they will be followed for approximately 10 years. It is expected that this study will provide more conclusive information about dietary fat as a risk factor for breast cancer. It is also expected that not all subjects will attain a reduction of dietary fat intake to 20 percent of their calories, yielding a distribution from which the dose-response relation may be determined. NCI scientists also hope to gain some information from this study on the relation between dietary fat intake and colon cancer, although the study is designed to focus on breast cancer.

Dietary Fat and Coronary Heart Disease: NHLBI

Research sponsored by the National Heart, Lung, and Blood Institute (NHLBI) has identified three major controllable risk factors associated with increased incidence of coronary heart disease (CHD): high blood pressure, elevated serum cholesterol, and smoking. Dietary factors have been related at least in part to two of these three—high blood pressure and cholesterol levels. In the case of high blood pressure, high caloric intake leading to obesity and high sodium intake may be important factors. The cholesterol relationship may be mediated by diet, since consumption of foods high in total fat, saturated fat, and cholesterol may contribute to increased blood cholesterol concentrations. NHLBI has determined that there is an association between diet and blood cholesterol levels and a relation between high cholesterol levels and risk of developing CHD.

Hazard Identification

It has long been recognized from pathology studies that myocardial infarctions are caused by plaques of cholesterol and cholesterol esters in the coronary arteries. In addition, observational epidemiologic studies undertaken over the past 20 years have established that increased levels of plasma total cholesterol are associated with increased risk of CHD.

Moreover, epidemiologic studies of CHD in European countries during and immediately after World War II revealed an apparent large decrease in CHD mortality and suggested a link to dietary patterns. Although direct pathological assessment of mortality was limited, it was speculated that the reduction in CHD mortality was associated with a sharply reduced intake of total calories, fat (primarily saturated), and dietary cholesterol due to wartime shortages of butter, eggs, and meat. Although other factors may have been at work, these findings provided impetus to the dietary fat hypothesis and provided an indication that CHD could be prevented by dietary modification.

Hazard Characterization

Serum cholesterol levels are strongly correlated with risks of CHD. Suspicions about the relationship of CHD to dietary fat have been the focus of investigations since the early part of the century when the Anitchkow study showed arterial cholesterol buildup in rabbits fed high cholesterol diets. The most significant recent studies addressing this correlation are:

The Framingham Study. Lipid and lipoprotein values, including fasting triglycerides and low-density lipoproteins (LDL), high-density lipoproteins (HDL) and total cholesterol levels (TOTAL-C), were obtained on nearly 3,000 men and women ages 49 to 82 years, chiefly between 1969 and 1971, at Framingham, Massachusetts. In a follow-up period of approximately four years, the data collected established a direct association between both LDL and TOTAL-C and the incidence of CHD. It was also noted that HDL concentration had an inverse association with CHD incidence. Moderate elevations of serum cholesterol in the range of 250 to 350 mg/100 ml were associated with a risk of CHD between two and five times higher than that noted for values below the average of approximately 220 mg/100 ml.

The Multiple Risk Factor Intervention Trial (MRFIT). MRFIT was a randomized primary prevention trial to test the effect of a multifactor intervention program on mortality from CHD in nearly 13,000 high-risk men aged 35 to 57 years. Men were randomly assigned either to a special intervention (SI) program consisting of stepped-care treatment for hypertension, counseling for cigarette smoking, and dietary advice for lowering blood cholesterol levels, or the usual sources of health care (UC) in the community. Over an average follow-up period of seven years, risk factors declined in both groups, but to a greater degree for SI men. Differences in mortality rates from CHD, however, were not statistically significant. Three possible explanations for this failure to demonstrate effect on CHD were considered: (1) the overall intervention program, under these circumstances, may not affect CHD mortality; (2) the intervention used may affect CHD mortality, but the benefit was not observed in this trial of seven years average duration because statistical power was reduced by lower than expected mortality and considerable risk factor change in the UC (as well as SI) group; (3) measures to reduce cigarette smoking and to lower cholesterol levels may have reduced CHD mortality within subgroups on the SI cohort, with a possibly unfavorable response to any antihypertensive drug therapy in some hypertensive subjects. The investigators concluded that a combination of the latter two explanations was most likely at work.

Further analysis of the MRFIT data as a whole shows a positive continuous relation between blood cholesterol levels and CHD. This examination of the entire MRFIT population indicates that overall mortality rate decreases with cholesterol levels down to approximately 181 mg/dl, then increases; this increase at low levels appears to be due to cancer deaths.

The Lipid Research Centers–Coronary Primary Prevention Trial (LRC-CPPT). LRC-CPPT, a multicenter, randomized, double-blind study, tested the effect of a drug that lowers blood cholesterol on the risk of CHD in 3,806 asymptomatic, middle-aged men with primary hypercholesterolemia (type II hyperlipoproteinemia). Subjects were divided into a treatment group that received a bile acid sequestrant (cholestyramine resin) and a control group that received a placebo, each for an average of 7.4 years. Both groups followed a moderate cholesterol-lowering diet. Mean falls of 8 percent and 12 percent in TOTAL-C and LDL-C in cholestyramine-treated men, relative to levels in placebo-treated men, were accompanied by a 19 percent lower incidence of CHD. Within the cholestyramine treated group, each decrement of 8 percent in TOTAL-C or 11 percent in LDL-C levels was also associated with a 19 percent reduction in CHD risk. The CHD incidence in men who achieved a fall of 25 percent in TOTAL-C or 35 percent in LDL-C levels (typical responses to the prescribed dosage (24 g/day) of cholestyramine resin) was half that in men whose serum lipids remained at pretreatment levels. Adherence to medication was associated with a reduced incidence of CHD only when accompanied by falls in TOTAL-C and LDL-C levels. Small increases in HDL-C levels, which accompanied cholestyramine treatment, independently accounted for a 2 percent reduction in CHD risk. Thus it appears that the lower incidence of CHD in the cholestyramine group was a result of lower TOTAL-C and LDL-C levels.

Supplementing these three major studies of cholesterol and CHD are many clinical and animal studies of associations between dietary cholesterol intake (sometimes including measurements of serum cholesterol levels) and incidence of CHD. For the most part, these experiments have not established a clear dose-response relation between cholesterol in diet and serum cholesterol, perhaps because of the high variability in response in animals and humans and the substantial endogenous production and removal of cholesterol.

Animal species vary widely in their response to dietary cholesterol, and it is not certain which species' responses most closely approximate those of humans. Many species respond to dietary cholesterol with an increase in plasma cholesterol concentration, followed by the development of lesions in the aorta, coronary arteries, and peripheral arteries that are similar to those of human atherosclerosis. In most experiments the type and/or quantity of dietary fat have also varied, but the addition of cholesterol to the diet has usually been necessary for the production of experimental atherosclerosis. A few experimental animals have developed myocardial infarction or gangrene of an extremity after prolonged consumption of high-cholesterol diets. Regression of lesions induced in animals by dietary cholesterol also occurs, but few studies have tested the effects of cholesterol removal alone.

Small-scale clinical studies have shown that human serum cholesterol response to dietary cholesterol varies greatly among individuals, as well as according to the quality and quantity of dietary fats. In general, the evidence indicates that in healthy adults who are "normolipidemic" by United States standards, plasma cholesterol concentration increases with increasing cholesterol intake over a range of doses from 0 to 600 mg/day. Some studies estimate that, in this range, each additional 100 mg dietary cholesterol per 1,000 kcal increases the average plasma cholesterol by 3 to 12 mg/dl. However, other studies have found no such effect. At the fifth biennial examination (1957 to 1960) the Framingham Study examined the relationship of cholesterol intake to serum cholesterol in 912 subjects. Men consumed, on the average, 704 mg cholesterol per day (range about 250 to 150 mg/day); and women, 492 mg/day (range about 150 to 1300 mg/day). No association could be identified between cholesterol intake and serum cholesterol levels. In a few studies that have tested the effects of different types of dietary fats, the addition of cholesterol to a diet high in saturated fats has led to a slightly larger increase in plasma cholesterol concentration than when cholesterol was added to a diet high in unsaturated fats.

Many small studies show an association between the ratio of dietary polyunsaturated fats to saturated fats (P/S) and decreased serum cholesterol. Populations on diets low in both saturated fat and cholesterol have low serum cholesterol levels; animals fed milk, meat, and egg diets have developed CHD; and normal human males on a diet with a P/S ratio of 4/1 show a reduction of TOTAL-C, LDL-C, and HDL-C compared to men on a diet with a P/S ratio of 1/4. However, both the benefits of lowered HDL-C and the mechanism of cholesterol lowering by unsaturated fats are disputed. The MRFIT study, in which some subjects followed a serum cholesterol lowering diet that consisted of increased unsaturated fat intake and decreased saturated fat intake, failed to show significant cholesterol lowering. However, many studies have shown that some individuals can lower their serum cholesterol levels with reduced cholesterol intake. The mechanisms of cholesterol metabolism are not well understood.

Exposure Characterization

Americans take in approximately 40 percent of their calories as fat, including saturated fat, monounsaturated fat, polyunsaturated fat, and cholesterol. Except for eggs, the intake of cholesterol and saturated fat are closely associated in most diets. Eggs contribute about 46 percent of the total cholesterol, but only about 4 percent of total fat and 3 percent of saturated fat to the average American diet.

People with more or less similar diets differ widely in their serum cholesterol levels; serum cholesterol levels have also been shown to vary with age. In economically less developed nations, clinically normal people who ingest predominantly vegetarian diets low in cholesterol, lipids, and calories had mean cholesterol-lipid-betalipoprotein levels in plasma that were significantly lower than groups of clinically normal persons in the United States. A comparison of residents of a Boston commune on a vegetarian macrobiotic diet had a mean TOTAL-C of 126mg/dl, while an age-matched group from Framingham ingesting the usual American diet had a mean TOTAL-C of 184 mg/dl, a difference unaccountable by differences in body weight alone.

Risk Determination

At the Consensus Development Conference on Lowering Blood Cholesterol, December 10–12, 1984, an advisory panel determined from the results of the studies described that there is a causal relationship between blood cholesterol levels and CHD. The consensus panel recommended that individuals with moderate or high risk blood levels be intensively treated. The panel also recommended that intake of calories be reduced, if necessary, to correct obesity and adjust body weight. NHLBI supports the DHHS *Nutrition and Your Health—Dietary Guidelines for Americans* that advises people to "avoid too much fat, saturated fat, and cholesterol."

Accordingly, the NHLBI has undertaken a national cholesterol education program aimed at professionals and the public that will highlight the importance of blood cholesterol in heart disease and provide recommendations for reducing blood cholesterol levels.

Radioepidemiological Tables: NIH

The Orphan Drug Act of January 4, 1983 (Public Law 97-414) directed the Secretary of the DHHS to devise and publish radioepidemiological tables that estimate the likelihood that persons who had any radiation-related cancer, and who had received a specific radiation dose before the onset of cancer, developed the disease as a result of such exposure. The law further directed that the tables show the probability of causation for each type of cancer associated with radiation exposure at doses ranging from 1 millirad to 1,000 rads in terms of gender, age at exposure, and other categories determined to be relevant.

To carry out this congressional directive, the assistant secretary for health of the DHHS asked the director of the NIH to establish an ad hoc Working Group. The Working Group was established in the office of the director of the NIH. Eight persons were appointed to the Working Group for their expertise and competence in endocrinology, pathology, radioepidemiology, biostatistics, and radiobiology. The chair was a deputy director of the NIH.

In order to properly devise the radioepidemiologic tables and provide the scientific basis for the probabilities included in the tables, the Working Group agreed to develop a complete scientific document to accompany the tables. To the extent possible, the supplementary material would: (1) assess the credibility, validity, and degree of certainty associated with the tables; and (2) present the formulas used to estimate the probabilities of causation.

The Working Group held open meetings between April 1983 and September 1984. At the first meeting, the general structure and content of the document were established, and responsibility for writing sections of the report was distributed among the Working Group members. Later meetings helped to identify problems, resolve outstanding issues, and address the comments of outside reviewers. Disagreements over specific aspects of a working paper or the treatment of broader issues such as smoking and radiation were resolved through group consensus. Thus, meetings of the Working Group served both planning and consensus development functions. The Working Group developed a draft report of its assessment (July 1984) that was reviewed by an oversight committee appointed by the NAS. The following discussion is based on the proceedings of these meetings and on the Working Group's assessment described in the January 1985 *Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables*.

Hazard Identification

Evidence of an association between radiation exposure and increased incidence of cancer is provided by studies of many kinds, including those of:

- Workers who ingested radium or inhaled radon;
- The survivors of the atomic bombings of Hiroshima and Nagasaki and natives of the Marshall Islands who were exposed to radioactive fallout from a nuclear weapons test;
- Persons exposed to radioactive iodine for treatment of hyperthyroidism;
- Persons treated with x-rays for ankylosing spondylitis; and
- Persons fluoroscoped in the course of treatment for tuberculosis.

The Working Group concluded that "the association [between radiation and certain cancers] is so strong as to appear certain" for acute forms of leukemia, chronic myeloid leukemia, and female breast cancer. Factors used by the Working Group to qualitatively assess the strength of the association were:

Statistical Significance. This depends on the total number of cancer cases observed and the apparent size of the excess risk relative to the baseline risk. For a fixed number of cases, the strength of the association is greater if the excess risk is relatively large and, for a fixed relative excess, the association is more credible if the evidence is based on many cases.

Specificity. How certain is it that the association was not due to something else? Credibility is helped by comparison with a nonexposed population that is otherwise similar to the exposed population, especially in studies of medically exposed populations for which the conditions leading to exposure may themselves be related to the risk of subsequent cancer. Since population groups that have been exposed to radiation actually differ in many ways from the general population, differences in rates of disease from general population rates may be difficult to interpret or to attribute to the radiation exposure.

Dose Response. The level of risk should appear to increase with increasing radiation dose to the tissue of interest. Each of us is exposed to natural background radiation at the very least, and so the concept of increased risk from additional exposure involves the assumption of a gradient of risk with increasing exposure. An association of risk with level of exposure also increases confidence that the exposure is directly responsible for the increase in risk.

Consistency. Is the association seen in several exposed populations, and are the apparent excesses similar when such factors as dose, age, and period of observation have been taken into account? "Statistically significant" associations will occur as a consequence of mere chance in a small proportion of studies, and many different studies have been and are being done. Such spurious associations are much less likely to arise independently in many different populations exposed under different circumstances. We therefore tend to place most credence in associations that turn up frequently and under diverse circumstances of exposure, while distrusting isolated reports not verified by other experience.

The Working Group used these criteria to develop a list of cancers associated with radiation exposure: Leukemia (acute forms and chronic granulocytic), and cancers of the bone and joint, thyroid, breast, lung, esophagus, stomach, colon, liver, pancreas, kidney and urinary bladder, and salivary gland. The relation between exposure (dose) and the likelihood that a later cancer was caused by radiation exposure (termed "probability of causation" by the Working Group) was examined in the next step of the risk assessment for each of these types of cancers.

Hazard Characterization

Because the time constraints imposed by Congress and the small size of the Working Group ruled out a new analysis of current epidemiological data, the group found it necessary to draw on existing studies. Two sources stand out:

Biological Effects of Ionizing Radiation (BEIR). This was a series of studies conducted by the NRC. The reports compile and interpret the world's literature on long-term somatic and genetic risks to people exposed to ionizing radiation at low doses.

Surveillance, Epidemiology, and End Results (SEER). Monograph reports were developed by the NCI providing broadly based and detailed information on the incidence of and mortality from cancer in the United States. Data are classified according to sex, race, age, place of residence of patient, and anatomic site and histologic type of cancer.

These sources provide the best available estimates of cancer incidence in the United States, a necessary element in developing the radioepidemiologic tables. Nonetheless, the scope and structure of the data somewhat constrained the methods available to the Working Group as it tried to estimate radiation risks. The SEER data, for instance, group bones and joints together, so that the option of separating bones from joints (which seem to have different responses to radiation) was not available. When such situations arose, or when data were inadequate to make a conclusive decision, the Working Group explained the problem and the position it adopted for the report. Additional issues included (1) whether to use the linear or linear quadratic extrapolation model, (2) how to adjust for dose rate, and (3) whether the relative or absolute risk model should be adopted.

Selection of Extrapolation Model. The extrapolation models used by the Working Group were the simplest dose-effect models consistent with the human epidemiologic data. The linear quadratic model was used for all cancers except thyroid and breast, where the linear model was applied.

Correcting for Dose Rate. Citing the conclusions of several national and international bodies that radiation given at a low dose rate is considerably less carcinogenic than radiation delivered at a high rate, the Working Group concluded that if a linear quadratic model is used for extrapolation to low doses, no dose-rate correction is necessary, given a certain partitioning of protracted radiation. The Working Group justified the use of the linear model for breast and thyroid cancer, in part, by citing evidence that risk coefficents for breast cancer in A-bomb survivors are the same over the entire range of doses and that risk coefficents for thyroid cancer in children treated with high radiation doses for thymic enlargement are similar to those seen after lower doses; i.e., there is no apparent dose rate effect for these cancers.

Selecting a Relative Risk Versus an Absolute Risk Model. An additional assumption needed in estimating the probability that radiation caused a specific cancer is the relation between the number of cancers occurring in any given time interval after radiation and the number normally occurring in a similar population not exposed to radiation. Because available data support the relative-risk, time-response model, the Working Group adopted a relative-risk, time-projection model that states that, at any time after a latent period, a given dose of radiation increases the probability of developing cancer by a constant fraction. Leukemia development follows a wave-like pattern; this is the model used for that cancer.

Exposure Characterization

No exposure characterization was performed. Because of the specific charge to the Working Group, the end result of this step of the risk assessment is a series of tables that present numerical factors that are to be used in the final calculation for probability of causation, once the dose and other important determinants of outcome are known. These determinants are an aspect of exposure characterization, which must be performed for each individual case. As noted above, the characteristics of exposure to radiation—dose, age at which radiation was received, the latent period between exposure and cancer development, and the sex of the affected individual—would all be factored into estimates of the probability of causation using the standard values developed by the Working Group.

Risk Determination

A final risk determination was not presented, though the tables are intended to be used by others for this purpose. The tables are constructed in a manner that permits probability of causation to be determined if information on individual exposure is available. The draft report includes examples of calculations to show how risk determinations should be made.

The discussion accompanying the tables highlights their uncertainties. Such a characterization of uncertainty is an important aspect of the risk determination step of a risk assessment. The areas of uncertainty discussed by the Working Group included:

- Sites of cancer and cell types,
- Source tables of cancer incidence,
- Coefficients describing dependence of risk on dose,
- Influence of age at exposure,
- Sex,

- Dosimetry,
- Dose-response function,
- Dose rate,
- Time-response models, and
- Differences in host factors determining susceptibility.

The draft includes a table that summarizes how these sources of uncertainty were handled and how their resolution may have influenced the estimates of probability of causation.

Finally, the draft discussion highlights the problems of determining individual causation. It stresses that probabilities calculated in this step of the assessment are useful for estimating how many of the cancers in some population group were likely to have been caused by radiation, but cautions that probabilities for a population cannot be applied to an individual to determine whether the cancer developed by that individual was caused by radiation exposure.

Cloning the Gene for Shiga-like Toxin: RAC

In September 1982, two investigators at the Uniformed Services University of the Health Sciences (USUHS) asked the NIH RAC to review and the NIH to approve cloning in *Escherichia coli* K-12, the structural gene of the Shiga-like toxin found in *E. coli*. The K-12 strain was proposed as the host-vector system because it does not colonize the human intestinal tract. The major risk of cloning the Shiga-like toxin is that its activity is similar to that of the *Shigella dysenteriae* toxin (Shiga toxin), a protein synthesis inhibitor. When administered parenterally, Shiga toxin is one of the most potent toxic proteins to humans. Thus, there was concern that cloning the Shiga-like toxin from *E. coli* might present hazards similar to those involved in cloning the *S. dysenteriae* toxin gene.

An initial review in September 1982 led the RAC to recommend that the cloning of the gene for Shiga-like toxin be performed only under the strictest physical containment conditions (P4). In December 1983 and again in April 1984, the experiment was resubmitted to the RAC for review in light of new information. The RAC Working Group on Toxins met on May 11, 1984, to review available scientific data and offer a recommendation to the RAC.

During these reviews, the USUHS scientists presented new evidence to support their claim that the proposed experiment could be performed safely at a lower containment level. The RAC and its working group of expert toxicologists used this information to reevaluate potential hazards that might result if the experiment were carried out at a lower containment level. The following discussion is based on summaries of the RAC meetings of February 6, 1984, and June 1, 1984, and the May 11, 1984, meeting of the RAC Working Group on Toxins.

Hazard Identification

Cloning the Shiga-like toxin from *E. coli* presents a potential hazard because its activity is similar to that of the Shiga toxin of *Shigella dysenteriae*, a potent toxic protein capable of causing severe reactions including death in humans.

Hazard Characterization

For cases where there is uncertainty about risk, the RAC adopts a position of "assume the worst," and places the burden of presenting evidence to the contrary on the researchers, in this case, USUHS scientists. The RAC reviewed and evaluated studies and other available information relevant to Shiga toxin and Shiga-like toxin, including data submitted by the applicants, additional information from RAC members, information forwarded to the RAC by its Working Group on Toxins, and information submitted by outside scientists responding to a notice published in the *Federal Register*. Discussion focused on the occurrence of the Shiga-like toxin genes (or genes that regulate its expression) and the toxicity of Shiga toxin.

Information concerning the widespread occurrence in nature of bacteria that produce Shiga-like toxins supported the applicants' claim that the proposed cloning would not introduce a new and "unique" organism into nature, citing the following:

- Clinical isolates of *E. coli* have already been shown to produce large amounts of a toxin that is indistinguishable biochemically and biologically from the toxin produced by *S. dysenteriae*.
- Many *E. coli* isolates, both pathogenic and nonpathogenic, express some toxin; therefore, "natural" and "shot-gun" cloning of *E. coli* DNA into *E. coli* have undoubtedly already resulted in cloning of the toxin gene.
- Strains of *Vibrio cholerae* produce Shiga-like toxin. Thus, genes for Shiga-like toxin are present in naturally occurring isolates of the family *Vibrionaceae* and are not restricted to the *Enterobacteriaceae*.
- Phages from two clinical isolates of *E. coli* control high-level

production of Shiga-like toxin in *E. coli* K-12 host strains by phage conversion. Thus, either the structural gene(s) for the Shiga-like toxin or regulatory genes that control high-level production of the toxin are present in wild-type phages from clinical isolates of *E. coli*. In this sense, "cloning" of genes that affect production of Shiga-like toxin onto phage genomes has already occurred in nature.

- Two of 15 normal human gut flora *E. coli* strains from asymptomatic infants produced low levels of Shiga-like toxin.
- Epidemiology studies of more than 150 *E. coli* strains isolated from human and animal stools have shown that 80 percent of the strains made detectable levels of Shiga-like toxin. Moreover, four of four substrains of *E. coli* K-12 make low levels of the toxin. Thus cloning of the Shiga-like toxin gene from clinical isolates of *E. coli* into laboratory strains of *E. coli* K-12 does not involve the introduction of a foreign toxin into the organism.

Points brought up concerning the toxicity of the Shiga toxin include:

- Shiga toxin is a potent cytotoxin for a subline of HeLa cells (a human cervical carcinoma tissue culture cell line), but the toxin has no effect on many other human, monkey, and rodent tissue culture cells. This activity against a limited spectrum suggests that the toxin would be nontoxic for most cells in the human body.
- Contrary to early reports, Shiga toxin is not a neurotoxin.
- The toxin administered intravenously is very toxic to rabbits and monkeys but not to mice. The monkey data, however, are a little "soft."
- Large amounts of Shiga-toxin (20,000 lethal doses for humans if the dose were administered intravenously) instilled directly into monkey intestinal pouches had no effect.

Exposure Characterization

RAC members evaluated the following information concerning the pathogenicity and toxicity of the Shiga-like, toxin-producing *E. coli*, and their relation to its invasive potential.

- Human volunteers fed large numbers of *S. dysenteriae 1* organisms that produced Shiga toxin but that could not colonize the bowel did not become ill. Therefore, any accidental ingestion of the organisms to be manufactured, a toxin-producing *E. coli* K-12 strain that cannot colonize the human intestinal tract, should pose little hazard to humans.

- Purification of Shiga toxin in several laboratories, and of *E. coli* Shiga-like toxin in the investigators' laboratory, has not identified any excessive risk from exposure to the toxin via the aerosol that is likely to be formed during the process of toxin preparation.
- Some strains of *Shigella* that produce Shiga-like toxin, but were not able to colonize the human gut, did not cause disease in volunteers. Thus the ability to produce Shiga-like toxin is not the sole virulence determinant in humans challenged by the oral route.
- There is no evidence that Shiga-like toxin causes disease in the way that botulinum or tetanus toxin can.
- Although shigellosis is a serious disease, it does not present a serious danger of epidemic.

Risk Determination

In its final recommendation concerning the proposed cloning of the Shiga-like toxin, the RAC decided that a P3 level of physical containment would be adequate. The perceived public health benefits of this particular experiment may have influenced the decisions of some RAC members to vote for a lower containment level, since performance of this experiment under less stringent containment conditions would facilitate research on the Shiga toxin gene, aid in the development of a live, attenuated cholera vaccine, and perhaps aid in developing a Shigella vaccine. Considerations such as these are usually assumed to be components of risk management rather than risk assessment; however, because the responsibilities of the RAC committee include certain risk management recommendations, such considerations are often a necessary component of RAC deliberations.

Based on the evidence that (1) the cloning of Shiga-like toxin would not produce a unique organism never found in nature; (2) the recombinant organism to be produced would not have invasive potential; (3) large amounts of Shiga toxin instilled directly into monkey intestinal pouches showed no effect, and (4) oral challenge of human subjects with bacterial strains that produce Shiga-like toxin but lack the ability to invade the gut mucosa did not produce disease symptoms, the RAC voted that USUHS researchers be allowed to proceed with cloning the gene for Shiga-like toxin under P3 + EKl conditions. This recommendation was submitted to the director of the NIH, who announced approval of the proposed research at the recommended level on September 13, 1984.

Carcinogenic Risks Associated with Mammography: OMAR

The first Consensus Development Conference activity was an examination of carcinogenic risks associated with mammography. In 1973, the Breast Cancer Detection Demonstration Projects (BCDDP) were initiated by the NCI and the American Cancer Society (ACS) to demonstrate the feasibility of screening large numbers of women for breast cancer using physical examination, x-ray mammography, and thermography. Almost 300,000 women were to be examined annually for five years using these three methods. Findings were to be made available to the screenees, and positive findings were to be forwarded to their physicians for diagnosis and treatment if necessary.

During the development and early phase of the BCDDP, several scientists raised questions about the use of mammography in large-scale screening programs. In late 1975, the concern was raised that "the routine use of mammography in screening asymptomatic women may eventually take almost as many lives as it saves." Not only was there no evidence that women under the age of 50 benefited from the radiation exposure or screening procedure, but the radiation associated with the use of mammography for detection of breast cancers might also trigger the development of breast cancer in some women. No concern was expressed or intended regarding the obvious value and importance of diagnostic x-ray examination of the breast in women with signs or symptoms that might be related to breast cancer.

To address these concerns, the NCI established three working groups to evaluate mammography as a screening tool on the basis of the apparent benefits of screening—evaluated mainly by a study by the Health Insurance Plan (HIP) of Greater New York—the possible radiation risks of mammography, and the nature of the lesions found by screening. This work was presented in the "Summary Report of NCI Ad Hoc Working Groups on Mammography in Screening for Breast Cancer."

In 1977 the NIH and the NCI established the NIH Consensus Panel for Breast Cancer Screening. The consensus panel was convened to develop a set of recommendations on the major issues and questions, focusing primarily on mammography, that had arisen concerning breast cancer screening and the BCDDP. The panel relied in part on results of another report on the screening program commissioned by the NCI—"Summary Report of the Working Group to Review the NCI-ACS BDCCP"—which was presented at the Consensus Development Conference.

Hazard Identification

Epidemiological studies of Japanese A-bomb survivors, former patients at Massachusetts tuberculosis sanatoria who received substantial cumulative breast doses from multiple fluoroscopic examinations, and women treated with x-rays for acute postpartum mastitis provided early indications that an increased risk of developing breast cancer was associated with irradiation of the breast.

Hazard Characterization

Studies of radiation-induced cancers in animals provided the following information:

- Females are consistently more susceptible to radiation carcinogenesis in the breast than are males.
- In rats, the carcinogenic effect of radiation on the breast is limited to breast tissue that is directly exposed and does not occur in neighboring or unirradiated portions of the breast.
- The incidence of breast tumors elicited by a given dose of radiation varies widely, depending on type of tumor, species, strain, and age of the animal at the time of irradiation.
- Data from rats have indicated a linear dose-incidence relation for mammary tumors.

In humans, studies of A-bomb survivors clearly demonstrate that females are more susceptible to radiation carcinogenesis in the breast than are males, and that age at exposure is an important determinant of subsequent risk. The epidemiologic studies showed a peak age of susceptibility to radiation damage between 10 and 19 years of age; the risk of radiation damage drops thereafter. According to this finding, within the population exposed to mammography younger women are at greater risk of radiation damage than are older women. Radiobiologic evidence used by the ad hoc Working Group indicated that calculations of dose-response relationships at doses below 100 rads should be based on a linear dose-response rather than a linear-quadratic dose-response. The average doses in the epidemiologic studies (about 1.5 rad per examination in the Massachusetts study, 100 rad in the mastitis study, and 66 rad for the A-bomb survivors) do not fall greatly outside the range of exposures in a long series of annual screenings. Only the study of A-bomb survivors is large enough to test the hypothesis of a linear dose-response. The evidence for a radiation effect at low dose levels does not depend on interpolation between values at 0 and 100+ rad doses, since actual observations at low dose levels (17 rads in the Japanese series) contribute to the evidence for a linearly increasing dose response at low dose levels.

Exposure Characterization

Radiation doses to the breast during mammography vary widely, depending on the characteristics of the film, the x-ray apparatus, and the operating techniques employed. The average absorbed dose is under 1 rad for each breast during a routine screening, but doses greater than 1 rad per examination were possible and in some cases doses were more than ten times greater.

Risk Determination

Ad Hoc Working Groups' Quantitative Assessment. The following factors were considered in the Ad Hoc Working Groups' assessment of risks associated with mammography:

- The duration of any latent period before the appearance of the radiation-induced excess in risk;
- The magnitude of the excess risk following the latent period;
- The change, if any, in the magnitude and time-distribution of the excess risk with variation in dose and dose rate; and
- The influence of age at irradiation on the radiation response.

By assuming that the dose-response from radiation during the mammographic procedure is linear with respect to dose, dose rate, and age at irradiation, the NCI Working Groups estimated the carcinogenic risks to the breast to be less than 1 percent for a single mammographic examination performed at age 35 with an average dose less than 1 rad. Thus, if a woman in the general population has about a 7 percent chance of developing cancer in her lifetime, one rad will increase her risk by 1 percent of 7 percent, or from 7 percent to 7.07 percent. The risk per examination becomes progressively smaller with increasing age at examination, but the total (lifetime) risk increases.

The NCI Working Groups estimated that the incremental risk of breast cancer in women at age 35 years or older per rad to both breasts from the tenth year after irradiation throughout the remainder of life to be 3.5 to 7.5 cases per million women over age 35. If this model is applied to 30,000 women at age 35 who receive four successive annual mammographies with an average dose to the breast of 2 rads per examination and live to the age of 75, it would project an increase of 25 to 54 cases (or 1 to 2 percent) in excess of the approximately 2,300 breast cancers expected to occur in the population through natural causes. For a women aged 35 who had a single mammogram, the lifetime probability of developing cancer would increase from 7.58 percent to 7.59–7.61 percent. For a million women, the corresponding risk would be 110 to 240 excess cases of cancer. If the examinations were annual, the average risk would increase to 7.90 to 8.25 percent for the individual, and approximately 310 to 670 cases of excess cancer in a million women could be induced.

Consensus Panel's Assessment. The Consensus Development Conference addressed the same issues and questions about large-scale mammography screening techniques for breast cancer detection that were addressed by the NCI Working Groups. The panel took into account the National Council for Radiation Protection (NCRP) evaluations of health risks from all forms of radiation exposure.

Evidence of the risks of mammography cited by the panel included: (1) the inherent risk of radiation exposure, (2) the particular susceptibility of breast tissue to radiation damage, (3) the linear relationship between dose and risk (one rad of exposure is estimated to increase a woman's risk of developing breast cancer by approximately 1 percent), and (4) the finding that the peak age of susceptibility to radiation damage is between 10 and 19 years, with decreasing susceptibility thereafter.

In discussing the benefits of mammography as a routine screening technique, the consensus panel found that the only sound scientific evidence that demonstrates that breast cancer screening has a favorable benefit is derived from a randomized controlled trial by the HIP of Greater New York that was begun in the early 1960s. The data from the HIP study showed that, for women over 50 years of age, combined use of physical examination and mammography as periodic screening techniques decreased the number of deaths due to breast cancer by approximately 40 percent. No benefit could be demonstrated for women 50 years of age or younger. Since they found no scientific data that demonstrate the effectiveness, or the extent of the benefit, of either mammography or physical examination as individual screening modalities, the consensus panel concluded that the benefit of the screening program rests on the use of physical examination and mammography in combination. Thus, it was not possible to state specifically how much mammography alone had contributed to the reduced risk. After weighing the relative risks and benefits, the consensus panel recommended that mammographic screening be reserved for women over the age of 50. However, throughout its deliberations, the panel repeatedly emphasized the distinction between mammography used for diagnosis—the value of which was not in question—and mammographic screening to detect possible disease in women who have no symptoms or physical findings whatsoever.

Analgesic-Associated Kidney Disease: OMAR

Ingestion of large amounts of some pain-relieving drugs over long periods of time has been shown to be associated with the development of one type of kidney disease that can lead to kidney failure. Since this problem was first reported in the 1950s, analgesic-associated kidney disease has become recognized as a significant, costly, and potentially preventable and treatable health problem. While research has shown an association of analgesic ingestion with kidney disease, debate continues about the specific drugs that cause it, the mechanisms leading to renal damage, and the extent to which this illness may contribute to the overall occurrence of renal disease. In February 1984, the NIH convened a Consensus Development Conference on Analgesic Associated Kidney Disease to review the data on the disease and prepare a risk determination.

Hazard Identification

Numerous case reports since 1950 have described a characteristic chronic tubulo-interstitial disease of the kidneys in patients who consumed large quantities of antipyretic analgesic mixtures, often in powder form. Epidemiologic support stems from studies in areas of high consumption outside the United States, correlations between increased incidence of analgesic nephropathy (AN) and high sale/consumption of analgesic mixtures, and suggestive evidence that heavy and sustained use of analgesic mixtures is associated with cancer of the urinary tract, especially transitional cell carcinoma of the renal pelvis.

Hazard Characterization

Although research studies in animals show that large doses of analgesics—including aspirin, phenacetin, acetaminophen, and their combinations—cause renal damage, debate continues about the role of specific drugs, the dose (exposure) necessary to cause these effects, and the mechanisms by which renal damage occurs. The quantitative relation between kidney disease and analgesic ingestion is unknown because too little information is available to estimate a dose-response or other quantitative measures of toxicity. Evidence for a possible mechanism of action suggests that the disease results from the effects of a toxic agent on the renal papilla; however, precise pathogenetic mechanisms are not known.

The adverse effects on the kidney appear to be the result of the use of analgesics in combinations:

- Reports of cases of AN in patients who ingested a single drug are rare.
- Most cases are associated with combinations of aspirin and phenacetin, but there are clear examples of cases of AN with other combinations of analgesics. It is possible that the mechanisms of renal damage may be the same in the latter cases, since these mixtures may contain one agent with an action similar to aspirin and one agent with an action simulating phenacetin.
- Regulatory removal of phenacetin from analgesic mixtures appears to have lowered the incidence of AN in Canada and in Scotland, but not appreciably in Australia. No explanation for this discrepancy is available; however, analgesic mixtures containing aspirin and acetaminophen are still commonly available in Australia.

Exposure Characterization

There are few data on the use of combination analgesics, especially regarding amount used. While it has been estimated that the prevalence of habitual consumption of analgesics ranges from 2 to 10 percent in the U.S. population, the proportion of analgesic users who develop AN is unknown.

Risk Determination

The Consensus Development Conference addressed the following questions:

- Can analgesics, alone or in combination, cause kidney disease and chronic kidney failure?
- What are the scope and characteristics of the problem of kidney disease caused by excessive use of analgesics in the United States and in other countries?

- What causes analgesic-associated kidney disease?
- Can it be prevented?
- What treatment strategies are appropriate?
- What are the directions for future research?

The first four of these questions are pertinent to the risk assessment process. In response to the first question, the panel concluded from a review of the evidence that (1) combinations of antipyretic analgesics taken in large doses over long periods of time can cause kidney disease and chronic renal failure and (2) there is no evidence that single antipyretic-analgesic drugs cause chronic renal disease when taken in doses recommended by physicians and/or drug manufacturers. The consensus panel also concluded, in response to the third question, that the hazard associated with the use of analgesics and kidney disease lies in the use of analgesics in combination, rather than as single agents. In response to the fourth question listed above the panel observed that, according to clinical observations, the risk of developing AN depends largely on the magnitude and duration of use of analgesic mixtures.

Based on the information summarized in the hazard identification, hazard characterization, and exposure characterization steps of the assessment, the panel reached an overall conclusion that "sustained use of mixtures of antipyretic analgesics in large doses is not advisable," and that the decision to limit over-the-counter products to single-analgesic compounds "should be considered."

Chapter 8

OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH

The Office of the Assistant Secretary for Health (OASH) is the focal point in the federal government for coordination and policy development of health-related activities. Its purpose is to promote improvements in health and health services. The OASH provides leadership and direction for the five Public Health Service (PHS) agencies and for several high priority, internal programs. The missions of five of these programs—the National Center for Health Statistics (NCHS), the National Center for Health Services Research and Health Care Technology Assessment (NCHSR/HCTA), the National Toxicology Program (NTP), the Committee for Coordination of Environmental and Related Programs (CCERP), and the Office on Smoking and Health (OSH)—routinely affect or result in risk assessments. General procedures and policies related to the conduct of risk assessment in these programs are presented in the Agency Overview sections of the chapter, and are followed by examples to highlight their analytic processes.

AGENCY OVERVIEW

Assessments Related to Medicare Coverage: NCHSR/HCTA

The National Center for Health Services Research and Health Care Technology Assessment (NCHSR/HCTA) is the focal point within the federal government for research on health care services. Projects range from clinically oriented studies of medical practice and medical technology to economic studies of the cost and financing of health care services. To carry out its mission of providing information to improve the effectiveness, efficiency, and distribution of health care services in this country, the NCHSR/HCTA supports a research grant and contract program, conducts intramural research, and disseminates the findings of health services research projects to state and local officials, policymakers, and program managers. The principal risk assessment activity within the NCHSR/HCTA is the assessment of the safety and efficacy of procedures considered by the Health Care Financing Administration (HCFA) for coverage by Medicare. This function is a major component in the program of health technology assessments conducted within the NCHSR/HCTA by the Office of Health Technology Assessment (OHTA). Health technology assessments also include consideration of the benefits of the technology under review, as well as a policy recommendation for the HCFA concerning Medicare coverage. The following discussion focuses primarily on safety assessments.

Mandate

Section 1862 (a) (1) of the Medicare Law, Public Law 89-97, prohibits payment under Medicare for health care items and services "that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." The HCFA interprets this language to include two basic criteria: (1) whether the procedure is safe and effective for its intended use and (2) the extent to which it has been commonly accepted for that purpose by the medical community.

In order to assist the HCFA in deciding what diagnostic and therapeutic techniques should be covered by Medicare, the OHTA evaluates selected technologies and develops recommendations on the appropriateness of payment. However, the HCFA, *not* the OHTA, is required by statute and regulation to make decisions on coverage. The OHTA evaluations are conducted under the authority of the Public Health Service Act, Sections 304, 305, and 308, as amended. Among other support roles, the OHTA participates in the NCHSR/HCTA extramural grant process and provides technical assistance to those who request it.

Organizational Placement

The OHTA is one of six divisions within the NCHSR/HCTA of the OASH. The responsibility in the HCFA for determining the safety and effectiveness of procedures considered for Medicare coverage lies in the Bureau of Eligibility, Reimbursement and Coverage (BERC). BERC interprets the provisions of the Medicare law pertaining to covered services, formulates policies based on the law, issues policy instructions to contractors, evaluates the adequacy of the program's coverage in terms of the health care needs of Medicare beneficiaries, and recommends changes in Medicare coverage and in program administration.

Agenda Setting

The term "health care technology" refers to any discrete, identifiable regimen or modality used to diagnose or treat illness, prevent disease, maintain patient well-being, or facilitate the provision of health care services. Questions regarding Medicare coverage or specific health care technologies are submitted to the OHTA solely by the HCFA, and the OHTA has no independent priority-setting functions. The agenda for HCFA review of new medical technologies is set largely by external requests to the HCFA for decisions on the effectiveness of existing technologies and of potentially promising experimental practices. For example, the OHTA makes periodic assessments of apheresis, an existing technology, but it also assessed Nuclear Magnetic Resonance Imaging as a promising experimental technology. Before the OHTA undertakes a full assessment of a technology, three requirements must ordinarily be met:

- The issue must be of national importance (e.g., a national Medicare instruction will be issued on completion of the PHS assessment);
- The technology must involve significant reimbursement expenditures for Medicare (e.g., the technology has the potential for rapid diffusion in a large patient population); and
- The data base must be adequate for an OHTA assessment (the definition of adequacy will vary according to the nature and course of the disease and the difficulty or complexity of the intervention in conducting clinical studies).

The OHTA begins by gathering preliminary information to determine the regulatory and scientific research status of the technology under consideration. If the OHTA receives information indicating that a particular assessment may not be appropriate at a given time, as when the treatment is currently under consideration by the Food and Drug Administration (FDA), the OHTA will recommend to the HCFA that the assessment be conducted at a later date. The HCFA is responsible for the actual priority determinations.

For most coverage decisions, the contractors which administer Medicare set their own policies, and coverage of a particular item or service may vary. However, a single national policy is sometimes developed because of serious questions about safety and effectiveness, or because the service or procedure has significant benefits and risks, so that to cover the service in some localities only would be unfair to Medicare beneficiaries there or elsewhere.

Each year, the HCFA receives between 100 and 200 requests for coverage decisions, most of which can be resolved by statute, regulations, or policy precedents. However, the resolution of some issues requires additional review. When HCFA staff have determined that medical advice is needed to reach a particular coverage decision, the issue is referred to the HCFA Physicians Panel composed of HCFA Central Office physicians and representatives from OHTA, and reviewed in order of request. The panel receives about 60 referrals a year and either resolves the question or recommends that it be referred to the OHTA. Approximately 25 of the 60 requests reviewed by the Physicians Panel are referred to the OHTA for full assessments.

Risk Assessment Methods

The HCFA's request for a technology assessment takes the form of a series of questions, developed by the Physicians Panel, regarding the safety and clinical effectiveness of the technology in question. While these questions do not follow any standard format, they generally include requests for information about indications for use of the technology, hazards associated with those indications, and comparisons of the technology with any existing techniques.

The OHTA assessment process begins with an exhaustive literature search and consultation with knowledgeable persons and groups. The next stage of the assessment is a synthesis of the accumulated information by OHTA staff to identify and characterize the nature and degree of benefits and attendant hazards. The synthesis leads to a comprehensive and detailed summary of pertinent published and unpublished information, including scientific and medical studies and expert opinions. Comments from authorities with the greatest degree of experience using the technology are accorded the most significance. After being consolidated and weighted according to its validity, the information is summarized in a report.

OHTA personnel generally rely on three types of studies to identify and characterize the benefits and risks associated with a medical technology:

- *Clinical trials* (controlled clinical experiments comparing one technology with another or with the absence of any technology) are generally the best measures of safety and efficacy, but are often not available.
- Well-designed *clinical studies* of the effects of a technology in practice provide important information about the safety and effectiveness of the technology under consideration. However, because variables such as patient selection are often uncontrolled, the results of such studies are generally less than definitive.
- *Qualified medical opinion* (testimonials) based on the judgments of clinicians concerning their experience with a technology is also of value. The OHTA specifically recognizes that such opinion is formed in the absence of experimental controls, collected unsystematically, and subject to unspecifiable bias. Hence this category of information is less useful in reaching conclusions regarding safety and effectiveness and usually receives appreciable weight only when more reliable data are not available.

OHTA assessments are generally qualitative in nature, but they may include some estimate of the number of people likely to be affected by the availability of a particular medical procedure. Recommendations concerning coverage consider possible benefits as well as possible risks.

In reaching its recommendation, the OHTA attempts to consider all reasonable combinations of treatment hazards with the settings in which a treatment might be used. The safety of a technology is expressed in terms of "relative risk," a comparison of the benefits of the treatment with the risks of existing treatments for the same indication or of no treatment, if none is established or appropriate. The OHTA uses three factors to determine what level of risk to the patient can be considered acceptable:

- The more severe the disease for which the technology is intended, the more acceptable are relatively unsafe technologies when no safer or more effective technologies are available.
- The more the clinical effectiveness of a technology is questioned, the less acceptable risk becomes, particularly when there is a body of evidence that suggests the technology may not be effective.

- The more inappropriate use of a technology is expected to occur the less acceptable risk becomes.

The OHTA staff person responsible for the assessment formulates conclusions and uses the available evidence about the technology's relative safety and effectiveness to develop an OHTA policy recommendation to the HCFA regarding the appropriateness of Medicare coverage for the technology. In this regard, OHTA technology assessments involve more than risk assessment; they also include policy recommendations. The OHTA may recommend that the technology not be covered by Medicare, that it be covered with stated restrictions, or that it be covered without restriction. If the technology in question is highly controversial, or if an existing treatment is satisfactory, the OHTA may recommend that more studies be conducted before a decision is made about Medicare coverage of the technology.

After the OHTA's assessment and recommendation have been made (usually twelve to eighteen months), the HCFA must make a coverage decision. Because the HCFA must often consider issues other than safety and effectiveness in reaching a coverage decision, the OHTA's recommendation, based primarily on safety and effectiveness, may or may not be accepted. If, for example, the OHTA has found that a procedure can be safely performed only in specific settings, the HCFA must determine whether it is administratively feasible to limit coverage in this way; or if the OHTA recommends coverage of a procedure only for specific diagnoses or indications, the HCFA must determine whether an attempt to limit claims payment would be so costly as to outweigh any benefit of coverage. Thus, the HCFA places the OHTA assessment in the context of health care policy decision making.

Scientific Review

Scientific review of OHTA reports is conducted by soliciting comments from OHTA staff and from staff of selected PHS agencies. The initial assessment takes the form of a draft report, which is circulated among the OHTA staff and the Department of Health and Human Services (DHHS) Technology Coordinating Committee for informal discussion and commentary. After this review, written comments on the revised draft assessment are selected from such experts as the NCHSR/HCTA division heads, the Office of Medical Applications of Research of the National Institutes of Health (NIH) (see Chapter 7), and scientists from other PHS agencies such as the FDA. The final version, which is modified to respond to any appropriate comments, is reviewed by the director of the OHTA and the director of the Technology Coordinating Committee.

Public Involvement

The public may become involved at three points in the Medicare coverage decision-making process described in this report:

- Requests for coverage decisions come from the "public"—usually Medicare carriers, but also physicians, industry, and other health care providers.
- Interested parties may respond to the *Federal Register* notice requesting comment on the technology.
- The public may request reevaluation after a decision has been made concerning coverage.

Description of Risk Assessment Reports

In the opening section of each technology assessment, the technology is described, along with its intended uses, conventional procedures that may achieve the same objectives, and the national demands or needs met by the technology. The rationale for the technology is then presented with an outline of the theoretical basis for the use of the technology for the particular indication. A summary of the available technical information addresses all published, peer-reviewed medical and scientific literature concerning the technology, including a comprehensive discussion of (1) the focus, design, and reliability of clinical studies; (2) known safety considerations and performance criteria; (3) comparisons noted between the new technology and conventional practices; (4) regulatory status of the product; and (5) any nonmedical or nonscientific controversies. Finally, a summary section presents the OHTA's recommendation along with key evidence used to support it and a discussion of the appropriateness of the technology in various settings. A listing of all references reviewed in the assessment is attached.

Mechanisms for Forwarding Results for Policy Decisions

The OHTA submits all technology assessments and coverage recommendations to the HCFA. After the actual decisions on coverage are made by the HCFA administrator or the secretary, Medicare contractors are notified.

Procedures for Disseminating Findings to the Public

After the HCFA has made a Medicare coverage decision for a particular technology, the OHTA synthesis and findings are routinely distributed to all sources for the report and to a standard mailing list of insurance and health care industry groups. In addition, the assessment reports are made available to the public. These reports provide valuable information to practitioners and to government agencies having an interest in a particular health care treatment or product.

Evaluation of the Public Health Effects of Assessments

After a coverage decision has been made and the technology assessment report has been released, comments on the report are received and reviewed by the HCFA and the OHTA. This review sometimes leads to requests for reassessment. When new clinical data on a technology become available, the HCFA may also request that the OHTA conduct a reassessment. In such cases, the OHTA first asks other PHS agencies to review the new evidence, then synthesizes the findings and develops a position on the need for a reassessment. The HCFA Physicians Panel considers the recommendation and determines whether a reassessment is warranted. If necessary, the OHTA initiates the data-gathering process for a revised assessment.

In 1984, for example, the HCFA requested that the OHTA make a reassessment of apheresis for the treatment of Goodpasture's syndrome. Originally it was recommended that this treatment be approved for coverage only as a last resort. However, when additional information became available indicating that the treatment might also be applicable for patients at earlier stages of illness, the HCFA Physicians Panel determined that the OHTA should conduct a reassessment. Instructions to extend this coverage were issued in September 1984.

In another 1984 case, proponents of percutaneous transluminal coronary angioplasty, originally recommended to be covered for stenotic lesions of a single coronary artery, argued that it might be safe for persons having multivessel disease. Their arguments persuaded the HCFA Physicians Panel that the OHTA should conduct a reassessment.

Several studies are currently under way to evaluate the results of coverage decisions in terms of utilization of medical services. One of these studies conducted by the congressional Office of Technology Assessment (OTA) found that "Medicare policies affect the adoption and use of medical technologies and the patterns of use of medical technologies significantly affect Medicare costs."

Disease Surveillance and Risk Factor Identification: NCHS

The National Center for Health Statistics (NCHS), the central focus of health statistics collection in the federal government, develops descriptive data for a wide variety of users, including those involved in identifying risk factors associated with adverse health effects. While only a small part of NCHS resources are devoted to research on risk factors in human disease or on exposure, NCHS data are widely used by others in this type of research.

Mandate

Formed in 1960, the NCHS is presently authorized to collect data in the following areas:

- The extent and nature of illness and disability in the population of the United States and its subgroups.
- The impact of illness and disability on the economy of the United States and on the well-being of the population.
- Environmental, social, and other health hazards.
- Determinants of health.
- Health resources, including the number of health professionals by specialty and type of practice, and the supply of services by hospitals, extended care facilities, home health agencies, and other health institutions.
- Utilization of health care, including utilization of ambulatory health services, services of hospitals, extended care facilities, home health agencies, and other institutions.
- Health care costs and financing.
- Family formation, growth, and dissolution.
- National vital statistics such as births, deaths, marriages, and divorces.

Organizational Placement

The NCHS is located in the OASH and has four program offices: Vital and Health Care Statistics Program, Interview and Examination Statistics Program, Data Processing and Services Program, and Analysis and Epidemiology Program. The Interview and Examination Statistics Program administers the population-based surveys conducted by the NCHS.

Agenda Setting

Formal mechanisms help the center identify major topics for data collection. Advisory groups provide recommendations for the design, content, and conduct of its broad surveys as well as for more specific surveys such as the Natality and Fetal Mortality Follow-back Survey. The National Committee on Vital and Health Statistics and its subcommittees provide recommendations to the center, as does the Committee on National Statistics of the National Academy of Sciences (NAS). The center conducts periodic solicitations for future topics for the National Health Interview Survey (NHIS). Inputs from other agencies may come through senior staff of the center, who serve on numerous interagency committees with responsibilities related to health data. The center has helped to develop the objectives for the Health Promotion Initiative, while the center director serves as cochair of the PHS Health Data Policy Committee. Within the center, resource allocations are determined primarily by the office of the director and the policy staff (center associate directors). Proposed topic priorities are also reviewed by the PHS Health Data Policy Committee.

Risk Assessment Methods

At the NCHS hazard identification, hazard characterization, and exposure characterization are carried out through national probability surveys of human health, behavioral characteristics, and other health-related topics. Several studies that involve these components include the following:

National Natality and Fetal Mortality Follow-back Surveys. These recurrent surveys collect data on socioeconomic and demographic characteristics of mothers, prenatal care, pregnancy history, occupational background, health status of mother and infant, and types and sources of medical care received. The most recent survey, which covered about 10,000 births and 7,000 fetal deaths occurring in 1980, collected data on consumption of alcohol, exposure to ultrasound, and nuclear medicine during pregnancy, among other items. Preliminary analysis revealed that women who smoke have smaller babies than those who do not. Further analyses will search for additional consequences of cigarette smoke, alcohol, and other risk factors on birth outcome.

National Survey of Personal Health Practices and Consequences. Data were collected on personal health practices, self-perceived health status, health care utilization, social support from relatives and friends, psychological factors, occupation-related health factors, life events, and selected sociodemographic characteristics. Results of the survey have been used to describe the distribution of and relations among various risk factors.

National Health Interview Survey (NHIS). For the past 25 years, this population-based household sample survey has collected a wide range of health data on both disease and the impact of disease (disability and health service uses) as well as selected exposure data. Examples of exposure data are cigarette smoking, alcohol consumption, exposure to x-rays, and the practice of selected preventive health behaviors. Data have routinely been collected on occupation and industry of the currently employed, providing information of potential relevance to the hazard identification and hazard characterization elements of health risk assessment.

National Health and Nutrition Examination Survey (NHANES) and Earlier Health Examination Surveys. These population-based sample surveys provide research data that can be obtained only through standardized examinations (e.g., extensive data on hypertension, serum cholesterol, heart disease, and diabetes). Exposure data are obtained by both questionnaire and clinical testing (e.g., blood, urinalysis). Examples of research using these data include studies of the effects of changes in the ozone layer and the incidence of skin cancer, analysis of carboxyhemoglobin levels relevant to the revision of the Clean Air Act, and analysis of serum lead levels. A special health and nutrition examination survey focusing on risk factors specific to persons of Hispanic origin was conducted in 1982–84.

NHANES I Epidemiologic Follow-up Study. In this study, participants in the 1971–75 NHANES I were reinterviewed between 1981–83 to collect data on health and hospitalization history since the earlier survey. These data will be used to determine the importance of selected risk factors on health status. Participants will be reinterviewed in the future, and also will be tracked through the National Death Index.

The findings compiled in these surveys have often been used in hazard characterization and exposure characterization.

Scientific Review

The scientific review of reports produced by NCHS staff is generally within the NCHS. Reports submitted for publication in peer-reviewed journals will have external review.

Public Involvement

The public has substantial input into the survey and risk assessment processes with respect to topics to be analyzed. Outside consultants, schools of public health, and physicians may make recommendations about types of data to be collected or risk factors to be measured. The Committee on National Statistics, housed at the NAS and supported in part by the NCHS, provides continuing high-level professional input.

Description of Risk Assessment Reports

NCHS survey findings are generally published in the *Vital and Health Statistics* series and *Advance Data* reports. These usually follow a defined format, beginning with a brief description of the analysis and results. A history of the subject matter follows, with references to previous studies or other supporting literature. The data used for the study are then reviewed, for their derivation, compilation, and extrapolation (including methods), to make estimates for the national population. The results of the survey are usually described in detail, including comparisons by such variables as race, age, and/or sex. Finally, a summary presents the conclusions along with the key supporting evidence. A bibliography or list of references is generally included.

Mechanisms for Forwarding Results for Policy Decisions

Selected NCHS survey results are summarized in the annual publication *Health—United States*, which is widely circulated throughout the federal government and the private sector. Because of the importance of NCHS survey data in epidemiologic research, the NCHS staff meet periodically with NIH staff involved in planning and reviewing epidemiologic studies; thus, NCHS findings may play a role in setting biomedical research policy. Government policymakers learn of NCHS results through conversations between NCHS staff and policymaking staff who sit on various interagency groups.

Procedures for Disseminating Findings to the Public

The center's data are used throughout the federal, academic, and private research community and are available through published reports, public-use microdata tapes, and special tabulations. Conferences are often held with data users, particularly data tape purchasers, to facilitate their use of the data and to assure improved use in the future. The majority of the center's data tapes are now distributed by the National Technical Information Service (NTIS). Tapes are also made available to all schools of public health for use by academic researchers.

Evaluation of Public Health Effects of Assessments

There are no formal mechanisms for evaluating the impact of NCHS surveys and studies on public health.

Assessment of the Adverse Effects of Chemicals: NTP

The National Toxicology Program (NTP) coordinates research and testing activities on potentially toxic chemicals and develops better, faster, and less expensive methods for quantitating chemical hazards. The NTP encompasses selected toxicologic activities of the NIH, the FDA, and the Centers for Disease Control (CDC). NTP studies often contribute to the first two steps of risk assessment and are used in the risk assessment process by many research and regulatory agencies.

Mandate

The (NTP) was established in November 1978 to (1) coordinate research and testing activities of the PHS, (2) provide information to regulatory and research agencies about potentially toxic chemicals, and (3) strengthen the science base of toxicology. NTP was granted permanent status by the secretary of the DHHS in October 1981.

NTP program objectives are to (1) broaden the spectrum of toxicologic information on environmental chemicals; (2) increase the number of chemicals tested, within funding limits; (3) develop, coordinate, and validate a series of tests and protocols to meet regulatory needs; and (4) communicate program plans and results to government agencies, the medical and scientific communities, and the public.

Organizational Placement

The NTP consists of the appropriate toxicology activities of NIH's National Institute of Environmental Health Sciences (NIEHS); the FDA's National Center for Toxicological Research (NCTR); and the CDC's National Institute for Occupational Safety and Health (NIOSH). The NIH component, NIEHS, provides the majority of the NTP budget, under the administrative and management control of the director, and houses NTP staff. The National Cancer Institutes (NCI) carcinogenesis bioassay program became part of NIEHS in July 1981, and the NCI remains active in NTP through membership on the Executive Committee. The NIOSH and the NCTR are not under NTP management; however, each cooperates with and participates in overall NTP activities. The director of the NTP reports to the assistant secretary for health of the DHHS.

Agenda Setting

The NTP executive committee, composed of heads of the research and regulatory agencies, provides primary oversight for the NTP and serves as the NTP's major advisory group. The committee advises the NTP director on research and testing needs and on selecting and setting priorities for the specific chemicals to be tested. It also serves as a forum for discussion of science policy issues and provides for timely information exchange among the various agencies. The committee provides continuing communication between member health research and health regulatory agencies, and receives advice about critical phases of its operation, including program planning and balance.

The NTP has a formal process both for the nomination and selection of chemicals and for studying the toxicology and potential hazards of chemicals. The selection process is initiated when member agencies of the NTP or other sources (federal agencies, state agencies, the public, labor, industry) submit nominations of chemicals for various types of toxicologic testing. Lists of chemicals nominated to the NTP are published in the *Federal Register* and public comment is invited.

Nominated chemicals are first reviewed by the NTP Chemical Selection Coordinator to determine which chemicals have been tested, are currently on test, or have been previously considered and rejected for testing by the NTP or its predecessors. Along with evaluated background literature and other available information, the nominations are prepared as draft executive summaries for each chemical by a support contractor.

The support contractor submits the draft executive summaries to the assistant director of the NTP for review. Following acceptance the summaries are forwarded to the Chemical Evaluation Committee (CEC), composed of representatives from the Consumer Product Safety Commission (CPSC), the Environmental Protection Agency (EPA), the FDA, the Occupational Safety and Health Administration (OSHA), the NCI, the NIEHS, the NIOSH, the NCTR, and the NTP. The CEC evaluates the draft executive summaries, recommends chemicals for study, suggests the types of toxicology studies to be performed, and assigns priorities.

The NTP Executive Committee operates under the principle that industry will test chemicals for health and environment effects as intended and mandated by Congress under legislative authorities. CEC recommendations are based on whether the chemical satisfies one or more of the eight NTP chemical selection principles:

- Chemicals found in the environment that are not clearly associated with commercial activities.
- Desirable substitutes for existing chemicals, particularly therapeutic agents, that might not be developed or tested without federal involvement.
- Chemicals that should be tested to improve scientific understanding of structure-activity relationships and thereby assist in defining groups of commercial chemicals that should be tested by industry.
- Certain chemicals tested by industry, or by others, the additional testing of which by the federal government is justified to verify the result.
- Previously tested chemicals for which other testing is desirable to cross-compare testing methods.
- "Old chemicals" that have a potential for significant human exposure and are of social importance, but generate too little revenue to support an adequate testing program (some of these may be "grandfathered" under FDA laws).
- Two or more chemicals together, when combined human exposure occurs (such testing probably cannot be required of industry if the products of different companies are involved).

- Marketed chemicals that have potential for large-scale and/or intense human exposure; in special situations, as determined by the Executive Committee, even if it may be possible to require industry to perform the testing (NTP, 1984).

The CEC's recommendations are reviewed by the NTP Board of Scientific counselors, and the board's ratings and comments as well as any pertinent public input are incorporated by the support contractor into final executive summaries. These are submitted to the NTP Executive Committee, which is composed of representatives of the CPSC, OSH, DHHS, NCI, FDA, NIOSH, NIEHS, EPA, and NIH. Executive Committee decisions on whether to study, defer, or delete nominated chemicals for the various types of toxicologic characterizations are published in the *NTP Annual Plans and Technical Bulletin*.

The selection of a chemical by the Executive Committee does not automatically commit the NTP to testing the chemical. The NTP is committed only to (1) ascertain the specific toxicologic and regulatory concerns; (2) evaluate the adequacy of existing data or current efforts in government, academic, or private laboratories; and (3) propose and conduct specific tests that are needed. Occasionally, new information from other sources answers the questions posed in the nomination and selection process. Sometimes testing is not done because chemicals are withdrawn by the nominator, because others are or will be testing the chemical, or because the chemical is not available or is no longer produced.

If NTP staff feel that the Executive Committee's testing recommendations have already been addressed or may not achieve the desired goals, the NTP staff may ask for reconsideration of the subject nominations.

Risk Assessment Methods

Toxicology research and testing activities within the NTP are divided into five program areas: cellular and genetic toxicology (mutagenesis); reproductive and developmental toxicology (fertility and reproduction); carcinogenesis; toxicology characterization; and chemical pathology. The first phase of toxicology characterization consists of in vitro studies and prechronic testing in experimental animals for up to six months. These composite data, which characterize the cellular and genetic toxicology of the reproductive assessment, and the shorter term in vivo findings of chemicals are used to select chemicals for further study and to aid in the design and interpretation of carcinogenesis and other appropriate toxicology studies. Chronic studies, primarily two years in length, are conducted for far fewer chemicals than the in vitro studies. For chronic effects, such as chronic toxicity and carcinogenesis, these tests constitute hazard identification. Most long-term studies developed during and after fiscal year 1982 include three dose levels plus controls in both sexes of two rodent species, with a 15-month interim sacrifice to provide more information on toxicity.

The NTP has adopted the following procedures for the design and conduct of the two-year studies:

- Each chemical is studied in both sexes in at least two species. Rats and mice are usually the species of choice.
- Each study usually contains at least 60 animals in each experimental group. When both sexes of two species are used and the substances are administered at four levels (including a zero control), 960 animals are needed.
- Exposure to the chemical is begun when the laboratory animals are about 7 weeks old. Mice and rats are usually exposed for 24 months.
- One treatment group receives an estimated maximum tolerated dose (EMTD), which is defined as the highest dose that can be given that is expected not to cause effects (other than cancer) that would alter the animals' normal lifespan. The other treatment groups are treated with fractions (usually ½ or less) of the EMTD.
- The route by which a chemical is administered is generally the same as or similar to the one by which human exposure is expected to occur.
- Animals are monitored throughout the study for signs of toxicity or other effects that may compromise their health.
- Maintenance of animals adheres to NIH guidelines and is under the direction of a scientist qualified in laboratory animal husbandry.
- Pathology is done by certified pathologists.

After a toxicology carcinogenesis study has been completed, a technical report is prepared by the NTP scientists responsible for that chemical. The results are evaluated and characterized according to one of five categories of interpretive conclusions for each study. These categories refer to the strength of the experimental evidence rather than to test chemical potency or mechanism of action:

- *Clear evidence of carcinogenicity* is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, a substantially increased incidence of benign neoplasms, or an increased incidence of a combination of malignant and benign neoplasms, where each increases with dose.

- *Some evidence of carcinogenicity* is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, marginal increases in neoplasms of several organs/tissues, or a slight increase in uncommon malignant or benign neoplasms.
- *Equivocal evidence of carcinogenicity* is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- *Inadequate study of carcinogenicity* is one that cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.
- *No evidence of carcinogenicity* is demonstrated by studies that are interpreted as showing no chemically related increases of malignant or benign neoplasms.

The conclusions reached using these categories of evidence constitute the final component of hazard characterization. All NTP toxicology and carcinogenesis studies technical reports include a statement that distinguishes between the conclusions drawn based on an NTP study and a risk determination:

> *Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazards to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis, which extends beyond the purview of this study.*

Scientific Review

The data from two-year experiments are evaluated and reviewed formally by senior NTP staff. After staff approval a meeting of a Peer Review Panel of the NTP Board of Scientific Counselors is organized. Notices of the meeting are published in the *Federal Register* and the *NTP Technical Bulletin*. At this time, draft technical reports are made available routinely to Executive Committee members, and agency staff, and to any individual or organization on request.

The Peer Review Panel comprised of 12 to 14 nongovernment scientists, critically reviews the draft reports in public session. Panel members give an oral critique together with a written statement detailing any deficiencies in design, conduct, or interpretation. Comments and questions are also requested from individuals or groups in attendance. Draft summary minutes for each technical report review are prepared and sent to the reviewers for necessary corrections and alterations. The edited minutes are then available for distribution to any interested party, and a highlighted summary appears in the first section of the printed technical report.

The technical reports are distributed to various government agencies and to those who request them. Approximately 300 technical reports have been printed and distributed since the first in 1976; the first 200 were done by the NCI and the more recent 100 were under the direction of the NTP.

Public Involvement

The public can participate in the chemical testing program at three points. At any time, any person or group may nominate chemicals for toxicologic study. After all nominations have been reviewed and the recommendations for testing announced, the public has 30 days to comment. Finally, the public is encouraged to attend and comment at the peer review meetings held to evaluate NTP draft technical reports.

Notices of public comment and peer review meetings are published in the *Federal Register* and in the *NTP Technical Bulletins*.

Description of Risk Assessment Reports

NTP technical reports are extensive and detailed. The preparation of each is a collaborative effort of a team of NTP senior scientists led by a chemical manager responsible for overall NTP activities for that chemical. A complete description of the materials and methods chosen for the study is provided in the technical report, including chemical structure, data recording, statistical methodology, fundamental assumptions, and relevant biological and environmental factors. Results are presented in a series of text descriptions, tables, and charts that compare body weight, clinical signs, survival, and pathology of the control and study animals. The report then discusses interpretations of the data and the conclusions drawn. NTP technical reports, ranging from 100 to 250 pages, also include references, a summary of the peer review panel's conclusions, and detailed appendices containing extensive data on individual animals, chemistry, and husbandry.

Mechanisms for Forwarding Results for Policy Decisions

The procedures used to inform government agencies about the results of studies of chemical toxicology depend on what indications of toxicity are found, and on how positive the evidence appears and how well the study was conducted. If the test results are judged to be clearly positive, the director of the NTP or the director of the Toxicology Research and Testing Program will send a preliminary notice to the assistant secretary of health, concerned regulatory agencies, and other key policymakers. The notice is usually sent to those people before the draft technical report on the chemical has been prepared and in advance of peer review by the board, sometimes as much as 12 to 18 months before a technical report is completed. In addition, regulatory agencies may contact NTP staff to monitor the progress of toxicology studies, especially for chemicals having a high index of human exposure.

Procedures for Disseminating Findings to the Public

The NTP uses several means to disseminate the results of the chemical toxicology research and testing program. The public information office handles most inquiries from the press and public and maintains the NTP mailing list of those who wish to receive specific types of information (e.g., those wanting all technical reports as printed). The *NTP Annual Plan,* a review of current and projected program plans, and *NTP Technical Bulletin,* an update on current program activities, provide information on NTP program reports. Results from the printed toxicology and carcinogenesis technical reports are announced in the *Federal Register,* while the NTP toxicology and carcinogenesis technical reports are made available for distribution and sale by the NTIS. A limited number of technical reports are available without charge from the NTP's public information office. The *Annual Report on Carcinogens* is prepared by the NTP staff and its member agencies for the secretary of the DHHS in response to a 1978 amendment to the Public Health Service Act (Section 301(b)(4)) that requires the secretary to publish annually a list of "substances which are either known to be carcinogens or which may reasonably be anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed." Each annual report also contains information on the nature and degree of exposure to such carcinogens and on the extent of federal regulation.

Evaluation of Public Health Effects of Assessments

Although the NTP has no formal mechanisms to determine the extent and means by which the results of the chemical testing program are used, some follow-up information comes to NTP by informal and voluntary communication from industry, regulatory agencies, and other sources.

Ad Hoc Risk Assessments of Chemical Exposures: CCERP

The DHHS Committee to Coordinate Environmental and Related Programs (CCERP), established by and reporting to the assistant secretary for health, consists of representatives from agencies within DHHS supporting or conducting environmental health, toxicology, and related programs. These include the NIH, Centers for Disease Control (CDC), and FDA, with liaison representatives from the CPSC, EPA, OSHA, Council on Environmental Quality (CEQ), Library of Congress, Departments of Energy, Army, Navy, Air Force, U.S. Environmental Hygiene Agency, and National Science Foundation (NSF). The CCERP promotes information exchange, sharing of resources, and coordination of programs related to environmental health and toxicology. On request from the assistant secretary for health or member agencies, the CCERP also provides advice, including development and review of risk assessments. The CCERP has established a standing Subcommittee for Ad Hoc Chemical Risk Assessments to fulfill its overall mission of assuring prompt, coordinated development or review of risk assessments among PHS agencies. The activities of this subcommittee are reviewed here.

Mandate

In order to fulfill its mission of coordinating PHS ad hoc risk assessments the subcommittee is charged by the assistant secretary of health to:

- Establish processes and procedures to assure rapid development or review of ad hoc chemical risk assessments, including outside peer review when appropriate;

- Enhance communications and information flow among various agencies concerned with risk assessments, and establish processes for anticipating and setting priorities among various risk assessments; and
- Recommend alterations in these procedures and processes as warranted.

Organizational Placement

The subcommittee reports to the chair of the CCERP, and consists of high-level representatives of the CDC, the FDA, the NIH, the Agency for Toxic Substances and Disease Registry (ATSDR), and the NTP. The subcommittee may establish ad hoc panels as necessary to perform risk assessment activities. The chair of the CCERP provides subcommittee reports to the assistant secretary for health who also serves as the chair of the CCERP executive committee. The CCERP executive committee is comprised of senior officials of PHS agencies concerned with environmental issues, including the director of the CDC, the commissioner of the FDA, and the director of the NIH.

Agenda Setting

The subcommittee responds to requests from PHS agencies or the assistant secretary for health. As of September 1984, the subcommittee had received one request (from the assistant secretary) for the development and review of risk assessments since it was established in January 1984. Other substances were under consideration by subcommittee member agencies.

Risk Assessment Methods

The one risk assessment developed to date by an ad hoc panel reporting to the CCERP subcommittee reviewed ethylene dibromide, in response to a request made by the OASH in early 1984.

Scientific Review

The subcommittee is charged to assure external peer review when appropriate. No formal external peer review was undertaken for the EDB risk assessment review.

Public Involvement

Risk assessments by the subcommittee have no regulatory status and are prepared solely for the use of the assistant secretary; no mechanism exists for public involvement.

Description of Risk Assessment Reports

The risk assessment review concerned with exposures to EDB:

- Reviewed the properties of EDB and data on its production and uses;
- Summarized existing laboratory animal data on EDB toxicity, carcinogenicity, mutagenicity, teratogenicity, and reproductive effects;
- Reviewed the limited epidemiologic data on carcinogenicity, teratology, and reproductive effects;
- Discussed the issues of EDB metabolism and tissue distribution; and
- Summarized existing EDB risk assessments, emphasizing some of the problems associated with the animal data bases which were used to develop these estimates.

Mechanism for Forwarding Results for Policy Decisions

Subcommittee reports are submitted to the chair of the CCERP, who forwards them to the assistant secretary for health and all appropriate agencies. In the case of the review of EDB, the chair of the CCERP transmits the report to the assistant secretary and the CCERP executive committee.

Procedures for Disseminating Findings to the Public

Reports are prepared solely for the assistant secretary for health, who may choose to disseminate the report to other interested parties or take other actions at his/her discretion. In the case of EDB, state health departments received copies of the assessment.

Evaluation of Public Health Effects of Assessments

No evaluation of CCERP assessments is proposed.

Effects of Smoking on Health: OSH

The Office of Smoking and Health (OSH) gathers and disseminates scientific information on the health hazards of smoking, for the purpose of reducing premature death and disability caused by cigarette smoking. One of the major functions of the OSH is to compile and submit to the secretary of the DHHS an annual report to Congress on the health consequences of smoking, as required by Public Law 91-222. In the development of these reports, especially as they pertain to risk assessment, certain analytic elements are considered.

Mandate

An annual report, *The Health Consequences of Smoking*, is prepared in accordance with the Public Health Cigarette Smoking Act of 1969 and its predecessor, the Federal Cigarette Labeling and Advertising Act.

Organizational Placement

The OSH is located in the OASH, DHHS. The Technical Information Center (TIC) is responsible for preparing and editing the annual report from draft sections submitted largely by individuals outside the DHHS.

Agenda Setting

Past reports have focused on such topics as smoking and women, smoking and cancer, and (in 1984) chronic obstructive lung disease. Selecting the focus of each report is an administrative process initiated by the OSH director and senior staff members, who identify smoking-related health problems that have been studied but not comprehensively evaluated. After two or three options are chosen and a synopsis of each is written, options and supporting descriptions are combined and forwarded to the secretary of the DHHS, who decides which option will be developed in the annual report.

Risk Assessment Methods

Individual chapters or sections of the annual reports are developed under contract without specific guidelines concerning the analytic methods to be used, by authors chosen for their expertise and ability. The style and length of each manuscript is set in a formal contract between the OSH and each author. Within this framework, the initial development of each section is left to the discretion of its author after consultation with TIC staff and outside scientific advisors. In general, the review of evidence of possible adverse effects of smoking encompasses all relevant epidemiologic, clinical, animal, and in vitro studies. Epidemiologic investigations provide the most important aspects of the information comprising the hazard identification phase of this process, while data from clinical, animal, and in vitro studies are likely to help in hazard characterization. Risk determinations in the annual reports are largely in the summary chapters, which are developed by OSH staff and outside consultants and advisors. The summary contains the overall conclusions of the report and focuses on the strength of the association between cigarette smoke and the adverse health effects covered in the report. The OSH applies the following guidelines to reach conclusions of causality:

- *Consistency of association.* This criterion requires that diverse methods of study of an association should be observed by multiple investigators in different locations and situations, at different times, using different methods of study.
- *Strength of association.* The strength of the association is normally expressed as the ratio of disease rates for smokers to rates for nonsmokers. This "relative ratio" yields evidence on the size of the effect of a factor on disease occurrence that will not be obscured by another associated factor.
- *Specificity of association.* This criterion asks how well one component of an associated pair can predict the other. A nearly one-to-one relationship between the presence of an etiologic agent and disease strongly suggests a causal relationship.
- *Temporal relationship of association.* The criterion of temporal relationship requires that exposure to the suspect etiologic factor precede the occurrence of disease.
- *Coherence of association.* The final criterion for the appraisal of causal significance is the coherence of association with known facts in the natural history and biology of the disease. In order to establish coherence, other possible explanations for the association must be systematically considered.

Scientific Review

Each annual report is reviewed in three stages. In the first stage, after chapters are completed by their authors, they are examined by the OSH staff and consultants, and sent to peer reviewers for comment. These reviewers are three to five nongovernment members, chosen on the basis of their expertise and background to review the material covered in a specific manuscript. Comments from the reviewers are evaluated by the OSH staff and its advisors, and those deemed relevant and appropriate are incorporated into the report. Authors may be contacted for clarification but are generally not otherwise consulted in the peer review process. After each chapter has been reviewed and revised as appropriate, the chapters are assembled into a single document.

In the second stage of the review process, the assembled document is sent to a panel of approximately 12 senior reviewers. As a third stage, concurrent with this latter review, copies of the entire document are sent to various agencies within the PHS for their review and comment. Changes recommended by these reviewers are also incorporated into the draft report.

Public Involvement

The lay public is not involved in the initiation, development, or review of the annual report.

Description of Risk Assessment Reports

The annual report, *The Health Consequences of Smoking*, presents a comprehensive review of new and current information on the health effects of smoking. The purpose of each report is not to analyze raw data, but to draw correlations and conclusions about smoking from existing scientific studies. The 1982 report presented a comprehensive assessment of the relationship between tobacco use and various cancers, and the 1983 report examined this relationship for cardiovascular diseases. In 1984, the report contributed a state-of-the-art review of the relation between tobacco and chronic obstructive lung disease.

Reports vary in structure and content according to the subject they address, but usually include chapters on passive smoking and smoking cessation, as well as extensive bibliographies. The introduction to each report includes a section stating the conclusions in nontechnical language. Specific conclusions are also listed at the end of each chapter.

Mechanisms for Forwarding Risk Assessment Results for Policy Decisions

The Health Consequences of Smoking is well-known and widely circulated. Each report is submitted to the U.S. Congress as part of the DHHS's responsibility to report new and current information on the topic required by existing congressional legislation. Many relevant agencies, such as the NIH, Veterans' Administration (VA), CDC, Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), EPA, FDA, NCHSR/HCTA, NCHS, and others receive draft and final copies of the report and in many instances are involved in developing the report. Because no government agency has regulatory jurisdiction over the use of tobacco products, "policy" decisions are primarily aimed at research priorities and public education programs.

Procedures for Disseminating Findings to the Public

The OSH uses a variety of programs and formats to disseminate the findings in the annual reports and the results of individual studies on smoking and health. Television, radio, and printed materials are used to give both present and potential smokers facts about the hazards of smoking. The OSH also responds to about 30,000 public inquiries and 5,000 technical information requests annually. The report itself is disseminated through the TIC scientific and technical mailing list of over 6,000 individuals and institutions, in the U.S. and more than forty foreign countries.

Evaluation of the Public Health Effects of Assessments

There has been no effort to directly assess the impact of the annual report. Because OSH educational campaigns in radio, television, and print are only a few of the many factors that influence smoking behavior, direct attempts to measure impact would be difficult and probably unsuccessful. The OSH has undertaken broader impact assessments, such as monitoring the trends of smoking behavior and cessation.

Periodically the OSH conducts nationwide surveys on the use of tobacco. Surveys vary according to size and focus, but the general objective is to determine current tobacco use patterns and current attitudes, knowledge, and beliefs about smoking among various population groups in the U.S. Survey data provide information on current smoking patterns, which can be matched against previous surveys to reveal long-term trends in smoking behavior and tobacco-use patterns.

CASE STUDIES

Transplantation of the Liver: NCHSR/HCTA

The first human orthotopic liver transplant took place in 1963. By 1983, over 540 such operations had been carried out in four medical centers in the United States and Western Europe. Although the operation is technically feasible and interpretable results have been reported from all four primary transplant centers, controversy continues because the operation is expensive, extremely demanding, and available only in certain parts of the country. Other major concerns are: (1) the identification of patients who may benefit from liver transplantation; (2) the stage of liver disease at which transplantation should be performed; (3) the survival and clinical condition of patients beyond the initial year after transplantation; and (4) overall long-range benefits and risks of transplantation in the management of specific liver diseases.

Hazard Identification

NCHSR/HCTA's Office of Health Technology Assessment (OHTA) produced a Technology Assessment Report on liver transplantation in 1983. The OHTA assessment consisted principally of the identification and discussion of hazards associated with liver transplant surgery. The available evidence consisted of the judgments of surgeons concerning their experience with liver transplant techniques. These opinions are formed without experimental controls, are not collected on a systematic basis, and are subject to unspecifiable bias. However, in the absence of more reliable data from controlled clinical trials or well-designed studies of clinical practice, such reports from medical authorities experienced with the technique were used.

Identified adverse effects include postoperative renal failure, severe intestinal edema and congestion, and difficulties in reconstructing the biliary tract (leading to potentially fatal complications such as bile leakage, duct blockage, or duct necrosis). Another major complication is graft rejection; various immunosuppressive agents have achieved only limited success. According to the FDA Oncology Drug Committee, a combination of the immunosuppressant cyclosporin-A with steroids has shown the greatest success thus far. The overwhelming weight of evidence points to liver transplantation as extremely hazardous surgery, still in the experimental stage.

Hazard Characterization

Because of the small number of liver transplant operations performed to date, no comprehensive studies had compared the outcomes of liver transplant surgery for various classes of patients, different types of liver disease, or varying combinations of immunosuppressive agents. Therefore, adverse outcomes other than mortality and quality of life were not assessed. Mortality rates at various liver transplant centers showed improvement over the past 20 years, with recent figures for one- and two-year survival at about 62 to 70 percent and 60 percent, respectively. Characterization of the quality of life of liver patients was based solely on limited data on the number of days spent in the hospital. Recipients surviving more than one year spend a small proportion of their time in the hospital. This is probably because these data include initial as well as terminal hospitalization times; those who survive the first year will most likely spend less time per year in the hospital than those who do not. These findings may have limited applicability because of the numerous variables affecting the outcome of surgery, such as surgical technique, patient selection, and medication.

Exposure Characterization

Of the estimated 30,000 to 40,000 persons who die in the United States each year of end-stage liver disease, approximately 10 to 15 percent may meet existing criteria of acceptability for liver transplantation (4,000 to 4,700 persons each year).

Risk Determination

The final OHTA recommendation was based on balancing the risks of liver transplantation against the risks of not performing the surgery.

OHTA staff noted that current one- and two-year survival figures may sometimes justify the procedure as a last resort when alternative therapies are no longer effective, and the overall 70 percent, one-year survival rate is balanced against certain rapid death if no liver transplant is performed. Because of the substantial uncertainties associated with liver transplantation, the OHTA recommended that approval be limited to patients most likely to benefit from liver transplant surgery. Taken as a whole, the evidence led the OHTA to conclude that liver transplantation is technically feasible, extremely expensive, and very complicated, but can extend the lives of carefully selected patients with end-stage liver disease. The final recommendation was approval with the following two major restrictions:

- *Limitations on the setting in which liver transplant surgery should be performed.* OHTA recommended use of specially qualified liver transplant centers to provide the range of tertiary care services as well as tissue and blood banking support that liver replacement surgery may demand.
- *Limitations on acceptable candidates for liver transplant surgery.* Approval was limited to patients most likely to benefit from liver transplantation: children with extrahepatic biliary atresia or other forms of end-stage liver disease.

Percutaneous Transluminal Coronary Angioplasty: NCHSR/HCTA

Percutaneous transluminal coronary angioplasty (PTCA) is a nonoperative method of restoring blood flow through diseased segments of coronary arteries and ameliorating symptoms of myocardial ischemia. Under local anesthesia, a balloon catheter is inserted into the blocked artery and dilated rapidly, compressing the stenotic lesion and allowing for increased luminal diameter and improved blood flow. In 1982, the OHTA evaluated this treatment as an alternative to the more established coronary bypass operation.

Hazard Identification

Complications with PTCA were reported in 117 of 631 patients (18.5 percent) entered in a special National Heart, Lung, and Blood Institute (NHLBI) registry to collect data on PTCA. The complications associated with performing PTCA included the following:

- Peripheral embolization;
- Irregularity or roughness of the intima at the angioplasty site;
- Local dissection at the site of intended angioplasty frustrating the procedure;
- Thrombosis at the site of the dissection;
- Perforation of a vessel by a guide wire causing serious blood loss;
- Vessel spasm induced by manipulation of guide wires;
- Potential complications of anticoagulant therapy; and

- Manufacturing faults of the device or inadvertent overinflation resulting in balloon burst.

The major concern was traumatization of the vessel wall by expansion of the balloon, especially since animal studies had demonstrated histopathological effects of PTCA. However, plaque compression on the arterial wall had not been demonstrated in animals, and clinicians disagreed about whether compression was important in achieving successful PTCA. Because the mechanism of PTCA was still incompletely understood, animal studies evaluating its effects were difficult to interpret. Initial concern also focused on the small immediate mortality of 1 to 2 percent associated with this procedure.

Hazard Characterization

No controlled clinical trials or research studies had evaluated the hazards of PTCA, so the incidence of PTCA-associated complications was estimated from uncontrolled information about patients who had undergone the procedure. In 1980, an analysis of NHLBI Registry data showed that in 6 to 8 percent of patients, sudden occlusion or deterioration of flow at the site of attempted PTCA resulted in persistent pain or impending myocardial infarction, necessitating immediate emergency coronary bypass surgery. Additional experience and a larger data base placed the incidence rate at 6.3 percent by 1982. The analysis of 1980 registry information also revealed that hospital deaths occurred in less than 1 percent of patients, with an incidence of 0.8 percent in patients with single vessel disease and 2.6 percent in those with multivessel disease. The mortality rate appeared to be higher in patients who had had previous bypass surgery, perhaps because of the increased risk associated with reoperation. The incidence of other complications of PTCA, including ventricular arrhythmias, hypotension, blood loss, and arterial thrombosis, appeared to be similar to the frequency of these complications with other vascular techniques such as cardiac catherization and coronary angiography.

Exposure Characterization

The technology assessment report did not provide a numeric estimate of the population of patients who might be candidates for PTCA. The number of such patients would depend on selection criteria and prevailing indications for bypass surgery. On the basis of these considerations, the report estimated that 5 to 10 percent of patients who have indications for coronary bypass surgery may be suitable candidates for PTCA.

Risk Determination

The clinical evidence and medical opinions evaluated by the OHTA pointed to PTCA as a promising but controversial technology. These data supported the safety and effectiveness of the procedure itself, although the complication rate was not inconsequential and the long-term safety of the procedure could not be determined. The report noted achievement of a success rate from 60 to 80 percent in a small group of patients unresponsive to medical management of coronary disease and who might otherwise undergo coronary bypass surgery. OHTA recognized that for this group of patients there is an approximate 1 percent risk of mortality. Therefore, the report concluded that PTCA appeared to be a reasonable alternative to coronary bypass surgery for such patients and that the procedure be approved for Medicare coverage by the HCFA. In view of the limited long-term data, however, the report recommended reevaluation of PTCA in two years when more definitive information would be available. In response to regional and physician contact reporting advances in this modality, PTCA was referred to the OHTA for reassessment in September 1984. The reassessment, in progress as of December 1984, focuses on review of specific patient selection criteria and on use of PTCA for multivessel disease.

Lead Exposure: NCHS

Lead has long been known to be toxic to humans, and exposures to lead are currently regulated by several federal agencies. One measure of exposure is blood lead level. The second National Health and Nutrition Examination Survey (NHANES II), conducted by the NCHS and the CDC, measured blood lead levels in the general U.S. population between 1976 and 1980.

Data on blood lead levels from the NHANES II were analyzed by the Division of Health Examination Statistics of the NCHS and the Division of Clinical Chemistry of CDC's Center for Environmental Health (CEH). Two types of analyses were conducted—an analysis of the association of selected demographic and socioeconomic factors with blood lead levels and a study of chronological trends in blood lead levels. Both are components of the exposure characterization of risk assessment.

Hazard Identification and Hazard Characterization

These were not considered in the NCHS analysis.

Exposure Characterization

In the NCHS analysis, the association of elevated blood lead levels with various demographic and socioeconomic factors indicated that some population groups are at substantially above-average risk of the adverse effects of lead. In this analysis, the population was divided into three age groups: 6 months through 5 years, 6 through 17 years, and 18 through 74 years old. Within age groups the affects of four demographic variables (race, sex, income, and degree of urbanization) on blood lead levels were analyzed.

The statistical methods used in the analysis took into account the complexity of the data and survey design. Regression analysis was performed for each age group, with the effect of the demographic variable tested after the adjustments for age. Special categorical data analyses were used to study different subgroups in the population.

Significant differences were noted in blood lead levels of specific groups. Higher levels were noted in children under 6 than in those from 6 through 17. Higher levels were observed in urban populations, decreasing as the degree of urbanization declined. Levels were substantially higher among blacks than among whites, regardless of age, income, and degree of urbanization.

Black children aged 6 months through 5 years had blood lead levels six times higher than white children (highly urban black children had levels 3.8 times higher, black children from smaller cities and rural areas had levels 7.3 times higher). Preschool children, black and white, from families with incomes under $6,000 (1978 dollars) had higher levels than children from families with higher incomes. Significant differences were not observed to be sex-dependent. Average blood lead levels decreased in the period from February 1976 through February 1980, concurrent with a reduction over the same period in the amount of lead used in gasoline.

The analysis of blood lead levels accounted for demographic and socioeconomic differences by a piecewise (or segmental) linear regression model. Race, sex, age, region of the country, season, income, and degree of urbanization were included in the model because different groups of people were sampled during the four-year survey period.

The overall reduction in average blood lead levels during the four years was 37 percent. Subgroups defined by race, sex, and age showed reductions in levels ranging from 31 to 42 percent.

According to NCHS scientists, three factors could have contributed to the downward trend:

- Public awareness of lead toxicity and sources of lead;
- Decreasing amounts of lead in the diet; and,
- Decreasing use of lead in gasoline.

The first two possibilities were found to be less likely for two reasons. First, increased public awareness of the sources of lead, such as old paint, would not account for the rapid overall reductions because old paint is attributed to elevated blood levels in young children only. Second, the FDA has not noted any trends in its estimates of dietary lead intake.

In contrast, previous studies had indicated that leaded gasoline contributes to blood lead levels and that 90 percent of airborne lead emissions comes from leaded gasoline. The EPA has noted a 40 percent decrease in the amount of lead consumption in gasoline over the four-year period covered in the NHANES II.

Correlation coefficients between the total lead used in gasoline production during a six-month period and the average blood lead level during the same period were statistically significant. The strongest correlation was observed for children aged 6 months to 5 years old, who are also the most vulnerable to lead toxicity.

Risk Determination

No formal risk determinations were made in these reports. The data provided useful information for use by the EPA and other agencies to accelerate regulations on the elimination of leaded gasoline, to assess the possible impact of past programs and regulations, and to identify high-risk groups.

Pentachloroethane: NTP

As a part of the National Toxicology Program's (NTP) ongoing chemical testing program, the carcinogenic properties of pentachloroethane, a solvent used primarily in the manufacture of tetrachloroethylene, were tested in rats and mice. The tests began in 1977, and a final report of the results was published in April 1983. The following discussion describes the assessment of carcinogenicity performed by NTP scientists. The results of the NTP tests, which include components of the first two steps of risk assessment, can be used by regulatory agencies in the development of quantitative risk determinations.

Hazard Identification

Pentachloroethane vapor produces irritation of eyes and respiratory tract and mild narcosis in humans. Pentachloroethane did not induce any mutagenic response in *Salmonella typhimurium* (strains TA 98, 100, 1535, and 1537) with or without metabolic activation.

Carcinogenesis studies have shown that various chlorohydrocarbons, including chloroethylenes, chloroethanes, carbon tetrachloride, and chloroform, induce hepatocellular neoplasms in mice but have little or no carcinogenic effect on Osborne-Mendel or Fischer 344 rats; data are accumulating that these chemicals also cause a small yet consistent increase in kidney tumors in rats. Pentachloroethane was tested to assess the hypothesis that the absence of carcinogenic effects in Osborne-Mendel rats is a genetic phenomenon and to increase the data base on pentachloroethane.

Hazard Characterization

No effects were noted in rats or mice in the single-dose studies. The same dosage levels were chosen for the 14-day study for rats and mice due to lack of observed acute toxicity. In rats, deaths occurred at the 500 and 1,000 mg/kg/day doses, but no gross or microscopic lesions or changes were noted with any of the rats. A single mouse died at the 1,000 mg/kg/day dose, but no gross or microscopic lesions or changes were noted. Dosage selections for the 13-week study depended on survival and body weight gain. All rats survived the 13-week administration period, and no compound-related changes were noted. Body weight gains for rats were slightly depressed at the 250 mg/kg/day dose, which, combined with previous work on chlorinated ethenes, led to the selection of 75 and 150 mg/kg/day dose group for the two-year study in rats. Although one female mouse in the 500 mg/kg/day dose group died during week 13, the lack of gross or microscopic toxicity led to the selection of 250 and 500 mg/kg/day doses for the two-year study in mice.

Two-year survival of high-dose male and female rats was significantly lower than survival of controls. Reduced survival was also noted in the low-dose male rat group, but no differences were noted between low-dose female rats and controls. Survival of mice was significantly affected. Forty-two of 50 high-dose male mice were dead by week 41, and only 44 percent of the low-dose male mice survived to the end of the study. The early deaths and compound-related body weight decrements that were observed were interpreted as showing a cumulative toxic effect of pentachloroethane administration.

A significant dose-related increase in chronic diffuse inflammation of the kidneys (nephropathy) was noted in male rats. The difference between this lesion and the normal nephropathy of aging rats was noted, and both changes were seen in some dosed males. There was suggestive but not significant evidence of increased incidence in female rats. Renal papilla mineralization was observed in dosed male rats at a significantly increased incidence, but was not considered to be a direct effect of compound administration.

The reduced survival in high-dose male mice and the killing of 25 male controls at week 44 restricted the use of normal statistical methodology for these data. Tumor incidences in male mice were compared at 0-52 weeks, 53-103 weeks, and at terminal kill.

Female mice in the high- and low-dose groups showed a significantly higher incidence of hepatocellular carcinomas than controls. Low-dose males showed a similar significantly increased incidence. Decreased survival rates precluded the evaluation of lifetime incidence for high-dose males, but a significantly increased incidence of hepatocellular adenomas were noted in female mice. The incidence of hepatocellular carcinomas in this study's control animals was similar to that in historical controls. The report discussed the possibility that hexachloroethane, the major contaminant (4.2 percent) in the pentachloroethane sample, could have had an impact on the findings. Hexachloroethane has been found to induce hepatocellular carcinoma in mice but not rats. It is not clear whether the low doses of hexachloroethane at the observed combination level could have accounted for the results or whether there is a synergistic/additive interaction between hexachloroethane and pentachloroethane.

Further results were noted after peer review of the report. Some tubular-cell adenomas of the kidney were reported in male rats; these tumors are uncommon in male controls. The NTP considers these tumors an indication of a target organ for carcinogenicity in the rat, possibly associated with the pentachloroethane administration. This latter finding was not submitted to the Peer Review Panel (see Chapter 7) for corroboration.

Exposure Characterization and Risk Determination

These were not performed.

Ethylene Dibromide: CCERP

Ethylene dibromide (EDB), a chemical widely used in the fumigation of grain and produce, in gasoline, and for other purposes, causes cancer and other serious adverse health effects in laboratory animals. Reports that human exposure to EDB may pose significant health risks led to widespread public concern and regulatory interest in controlling such exposures. In early 1984, the assistant secretary for health asked the Committee to Coordinate Environmental and Related Programs (CCERP) to assess the risks associated with exposures to EDB. At that time, CCERP's standing Subcommittee on Ad Hoc Chemical Risk Assessment established an ad hoc panel consisting of the scientists from the NIOSH, the NIEHS, the FDA, the NCI, and the CDC, with representatives from the EPA as observers.

The panel divided the assessment into these six components: (1) properties, production and use, and environmental levels and exposures; (2) toxicity, carcinogenicity, and mutagenicity; (3) teratogenicity and reproductive effects in animals; (4) epidemiologic studies; (5) metabolism and tissue distribution; and (6) risk estimation. Individual panel members prepared specific components, which were reviewed at a meeting of the entire panel. The assessment also included quantitative risk determinations that had been developed by other government bodies, primarily the EPA and the NIOSH.

Hazard Identification

The first human exposure to EDB was reported in 1910, and the first occupational exposure in 1928. Animal toxicity studies were reported as early as 1927. Animal studies have reported toxic effects of EDB for acute, subchronic, and chronic exposure. Epidemiology studies of potentially exposed worker populations have not shown statistically significant increases in sterility, cancer, or mortality.

In 1974, the National Cancer Institute described a preliminary finding of EDB's carcinogenic activity in rats and mice, and in 1975 reported a final study that showed EDB to be carcinogenic in both rats and mice. In 1977, the NIOSH reported evidence of impaired fertility or complete sterility in men engaged in the production of dibromochloropropane (DBCP), a chemically related compound also used as a pesticide. In 1977, the NIOSH recommended lowering the OSHA standard for occupational exposure to EDB, based in large part on the evidence of irreversible genetic damage from EDB exposure.

Hazard Characterization

Inhalation and gavage studies in laboratory animals have demonstrated acute, subchronic, and chronic toxicity of EDB. Effects range from decreased weight gain with eye and lung irritation to neoplasia in several organs. Skin exposure caused carcinomas and other tumors.

EDB has mutagenic and genotoxic effects; however, EDB has not produced dominant-lethal mutations in rats or mice. Animal studies of teratogenicity and reproduction do not provide sufficient data to reach definitive conclusions about the impact of EDB.

Four epidemiologic studies of workers occupationally exposed to EDB have been reported, but substantial deficiencies, including lack of exposure data, inadequate sample sizes, and inappropriate cohort or control group selection, have limited their use in analyses of the evidence of human carcinogenicity. The panel stressed the inconclusive nature of the epidemiologic studies.

Exposure Characterization

Two aspects to the characterization of exposure were addressed in the panel's assessment: the number of people potentially exposed to EDB, and the likely doses of EDB for a given population. The panel cited previous estimates of the number of workers potentially exposed to EDB in two categories: (1) those potentially exposed during production and use of EDB (108,000) and (2) those potentially exposed from working with leaded gasoline (875,000). No estimate of the number of people exposed in the general population was discussed, except to note that it would presumably be at least one order of magnitude greater than the number exposed occupationally.

The panel did not develop its own exposure estimates, but exposures to EDB have been estimated by other agencies using EDB concentrations reported in food and environmental samples. Estimated exposures have been calculated for specific occupational exposures that include manufacturing processes; antiknock blending; gasoline stations; garage mechanics; and occupations in fumigation. Estimated exposures for the general public were based on exposures from food, water, and air. Among the dietary sources considered were flour, wheat, and citrus fruit. (It was noted that the EPA concentrated on wheat contamination exclusively in its food exposure assessment, since it makes up approximately 10 percent of the standard diet.)

Risk Determination

Based on its review of the data presented above, the panel concluded that "there is very little doubt that EDB is a toxic compound. It is mutagenic in multiple systems and it alkylates DNA. It is carcinogenic in both rats and mice and has produced tumors in one or both species by three different routes of exposure."

Although other agencies (e.g., the NIOSH and the EPA) have developed risk estimates for EDB, no quantitative carcinogenic risk determination was performed by the panel. The panel discussed the studies that had been used for EDB risk estimation and noted that several limitations created serious problems in determining the shape and slope of the dose-response curve and made quantitative risk estimation an uncertain process.

Adverse Health Effects of Passive Smoking: OSH

"Passing smoking" is defined as the exposure of nonsmokers to tobacco combustion products from the smoking of others. The possible adverse health effects of passive smoking have become a controversial and emotionally charged public health concern. The 1984 surgeon general's report on smoking and health, *Chronic Obstructive Lung Disease,* published by the Office on Smoking and Health (OSH), devotes one chapter to a review and evaluation of the data that relate passive smoking to the occurrence of physiologic changes, symptoms, and diseases in nonsmoking adults and children. The major conclusions concerning the adverse effects of passive smoking and the evidence relied upon to reach these conclusions are summarized in the following discussion.

Hazard Identification

Several studies have identified possible adverse effects on the respiratory system of passive smoking. These studies have shown a positive relation between parental smoking and the reporting of chronic cough, chronic phlegm, and persistent wheeze in children. Other relations between parental smoking and health of children have also been established. For example, young children with smoking parents have more respiratory illnesses in the first two years of life; this effect appears dose-related by numbers of parents smoking and by amount of time spent with a smoking mother.

Hazard Characterization

Studies aimed at further characterizing the pulmonary effects of passive smoking and providing dose-related information include the following:

- Three studies have utilized exposure chambers in studying the responses of nonsmoking adults to passive smoking. Passive smoke exposure to less than half a cigarette in two hours caused small but measurable changes in the airways of normal individuals.
- Pulmonary function was evaluated in adults exposed to environmental cigarette smoke. The results ranged from no effect to significant effect of office exposure. Differences in exposure variables, age of subjects, and characterization of the exposure may explain the range of outcomes.
- Pulmonary function in children is also related to smoking in the home, and maternal smoking may be the most important factor. Younger children are more affected than older children.
- Respiratory symptoms in children increase with an increase in the number of smoking parents in the home.
- Subjective eye irritations and blink rate increase with duration of exposure to environmental tobacco smoke. These responses were noted at levels lower than airway responses have been demonstrated.

Exposure Characterization

Passive smoking research deals with exposure that is different, both qualitatively and quantitatively, from that of active smoking. Measurements of human exposure to the constituents and byproducts of cigarette smoke through passive smoking have been difficult to develop for two reasons. First, some of the byproducts of tobacco smoke occur in indoor environments from other sources and are difficult to distinguish from the results of cigarette smoking. Second, individual exposures are influenced by such variables as number and type of cigarettes burned, size of room, ventilation rate, and smoke residence times.

Information on levels of exposure is summarized below:

- Some of the airborne products of tobacco smoke (including carbon monoxide, nitrogen oxide, nicotine, respirable particulates, nitrosamines, and aldehydes) are significantly elevated by indoor cigarette smoking.

- The nonsmoking population may be exposed to 0-14 mg of tar/day, with an average exposure of about 1.46 mg/day; the health risk posed by this exposure has not been determined.
- Studies in humans with biologic markers to assess chronic exposure have shown that urinary cotinine, a metabolite of nicotine, is elevated in nonsmokers who are exposed to cigarette smoke.

Risk Determination

Based on the above data, the OSH formed these conclusions:

- Cigarette smoke adds significantly to the level of indoor air pollution.
- Urinary cotinine, a metabolite of nicotine, is noted in nonsmokers who report exposure to environmental tobacco smoke.
- Some studies have noted small changes in pulmonary function due to high levels of passive smoking.
- Children of smoking parents have an increased number of respiratory symptoms and diseases early in life.
- Small but measurable differences exist in pulmonary function between children of smoking parents and children of nonsmoking parents.

This risk determination provides the basis for current OSH efforts to improve education related to passive smoking.

Chapter 9

ANALYSIS OF HEALTH RISK ASSESSMENT ACTIVITIES IN THE DHHS

Chapters 4 through 8 present a detailed overview of Department of Health and Human Services (DHHS) structures and processes for assessing health risks and indicate the dimensions and diversity of health risk assessments in the department. Each unit has important and unique features defined by its health mandate and its risk determination procedures. However, many common themes raise the issue of whether disparities can profitably be reduced, whether DHHS staff can make better use of generic features or operating conditions that underlie its separate risk assessment activities, and whether common factors can in some way help policymakers to understand better—and perhaps utilize better—departmental options and resources for managing health risks. This chapter applies the concepts and definition of Chapters 2 and 3 to the information presented in Chapters 4 through 8 to examine and draw conclusions about how risk assessments are developed and used by the DHHS and its agencies. Special attention is given to how DHHS agencies make determinations about health risks and how they structure managerial mechanisms for use at all levels of the department.

Each agency must respond to its own unique set of influences that, quite properly, shape the nature of the health risk assessments it needs. Factors affecting the observed differences include agency mandates for research vs. information transfer vs. regulation; prospective vs. retrospective purposes of assessments; focus on individual substances vs. disease incidence vs. lifestyle characteristics; biologic substances vs. synthetic chemicals vs. physical hazards; and intended use in priority setting vs. policy setting.

These and other categories are more fully discussed and characterized in the following sections.

COMPARISON OF AGENCY APPROACHES TO COMPONENTS OF RISK ASSESSMENT

The four-component framework of risk assessment (hazard identification, hazard characterization, exposure characterization, and risk determination) and the context of agency mandates serve as cornerstone concepts with which to analyze the DHHS health risk assessment process (see Chapter 3). Not all units perform all the steps of risk assessment. Furthermore, the nature of a unit, its mandates, and its historical and contemporary context all play a role in each risk assessment component that the unit undertakes. Within each step, however, some similarities and differences among various DHHS units are worthy of mention.

Hazard Identification

Five types of data are recognized as instrumental in determining risks: clinical; epidemiologic; those from whole animal studies; those from studies of cells, tissues, and organisms in culture; and those from investigations of mechanisms of action (see Exhibit 2–2). Another form of data considered in, but not pivotal to, risk determinations is structure-activity analysis. Depending on the kind of health risk, the purpose of the risk assessment, and the nature of the available data, some units rely more heavily on one type of data or another.

Human data used by various DHHS agencies include those from reports of accidental exposures, monitoring and surveillance of exposure, epidemiologic surveys (cohort and cross-sectional), case control investigations, and clinical studies. When epidemiologic or other human investigations yield convincing results, they are of great value because they provide information about humans under actual conditions of exposure to a specific agent. Thus, a sort of hierarchy of data emerges, with more weight given to results from definitive, well-designed, properly controlled human studies than to results from animal studies in the evaluation of hazardous properties and health risks, and to whole animal studies than to in vitro results.

While no study can provide a valid assurance of perfect safety, negative data from epidemiological studies of sufficient size can sometimes be used to establish an upper bound on risk, so that exposures below some specified level almost assuredly will not create serious harm. Although human studies are powerful when clear differences exist and are corroborated by other findings, such studies in general, and epidemiologic studies in particular, are often subject to uncertainties derived in part from the existence of confounding variables, from limitations on the accuracy of measurements, and from the long latency between exposure and manifestation of some important diseases.

Nearly all DHHS units place substantial emphasis on the acquisition and the application of human data. The National Center for Health Statistics (NCHS) of the Office of the Assistant Secretary for Health (OASH) is the central focus for the collection of population-based health statistics, while the National Institutes of Health (NIH) support a very large but almost completely decentralized effort in clinical statistics as well as some centralized survey and registry programs. The NCHS data cover a wide variety of topics, including data on consumption of alcohol and exposure to cigarette smoking, and are used extensively for risk assessments by scientists and policymakers in the federal government and elsewhere.

The Centers for Disease Control (CDC) collect data from human experience through its epidemic investigations and health hazard education and surveillance systems, which identify potential risks through the Birth Defects Monitoring Program, and localize infectious hazards in hospitals through the National Nosocomial Infections Surveillance System. The major risk identification techniques used by CDC's Center for Health Promotion and Education (CHPE) are surveillance and prevalence surveys, including the Behavioral Risk Factor Prevalence Survey, Puerto Rico Fertility and Family Planning Assessment, Nutrition Surveillance System, and Suicide Surveillance System, which are supported by epidemiologic studies to determine accurately the relative risks of identified risk factors. Human data obtained from surveillance of clinical reports of drug abuse and case reports of disease incidence serve as bases for the National Institute on Drug Abuse (NIDA) in the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) to select priority topics and for the CDC's Center for Infectious Diseases (CID) to conduct epidemiologic investigations.

Within the Food and Drug Administration (FDA), numerous activities use human data for hazard identification. An ongoing program catalogs and examines postmarket reports of adverse reactions to pharmaceutical agents, so that materials judged overly hazardous can be removed from the marketplace. This information also enables the FDA to offer guidance to consumers and physicians on how to protect themselves against unwanted effects of drugs judged to have essential benefits. The FDA also participates with other units of the DHHS, most notably the National Cancer Institute (NCI), in evaluating the merits of hypotheses linking medical ailments and diseases to dietary constituents, as in the epidemiologic study of bladder cancer and ingestion of artificial sweeteners.

The ADAMHA uses epidemiologic studies to identify the risks of behavioral characteristics and lifestyle choices. For example, the National Institute of Mental Health (NIMH) in the ADAMHA sponsors the Epidemiologic Catchment Area (ECA) program, a population-based epidemiologic study of mental disorders that is intended, in part, to examine hypotheses about risk factors for specific mental disorders. Also at the ADAMHA are the cohort studies supported by the NIDA to help identify the risk for homosexual men of acquiring AIDS.

Similar examples at the NIH include prospective and follow-up studies by the National Institute on Aging (NIA) to examine the effects of smoking, drug and alcohol use, weight and weight change, exercise, and blood pressure on such outcomes as illness, hospitalization, and death among elderly people; and a National Institute for Child Health and Human Development (NICHD) investigation of the causes of prematurity, low birth weight, birth defects, and mental retardation. Through its extramural grants program, the NIH sponsors in universities a vast array of human studies structured to provide clues on the sources of major diseases in our population. Other NIH resources for hazard identification are found in the substantial support of individual institutes for clinical statistics and survey efforts. Clinical studies also provide extensive data on the health risks apparent in the side effects of medical treatments.

Many of these sources of human data serve multiple uses, among which risk assessment for policy purposes, and hazard identification in particular, may be low in the order of priorities and interests. The data may not be entirely appropriate for many risk assessment purposes, and the potential value of some activities for risk assessment may be overlooked. For example, NCI-supported data on clinical trials are primarily used for the development of new therapies, and often do not include information relevant to risk factors for the occurrence of the condition treated. When such data have been collected and analyzed for risk indicators (e.g., by the Eastern Cooperative Oncology Group) they have proved quite productive. Similarly, the multipurpose NCHS (OASH) surveys can only occasionally explore in depth any one topic, such as tobacco use, so their contents may have limited potential as a sole basis for policy directives. However, such general purpose survey data are essential elements in many kinds of exposure assessment, and when both exposure and outcome data are collected in the same survey they may provide important information on the cause-effect relationships that are central to both risk assessment and risk management.

In many efforts of DHHS agencies to identify hazards, laboratory animals serve as useful surrogates to humans, especially in studying the toxic properties of chemical, physical, and microbial substances. Researchers turn to animal studies when human data are inadequate, when there are ethical prohibitions against obtaining human data, or when it is impractical, unfeasible, or unethical to obtain relevant data. For example, latent periods for some toxic effects in humans are measured in decades before the manifestation of disease, while the same effects in rodents are evident within 24 months. The interpretation of animal toxicity studies is based primarily on the long-standing assumption that effects in humans can be inferred from effects observed in animals and that important basic anatomical, physiologic, and biochemical parameters tend to be similar across mammalian species. Some features are known or assumed to extend more broadly, as in the Ames test, which uses a bacterium to infer carcinogenicity.

The assumption that animal effects predict human effects has two main foundations: current understanding of the evolutionary relationships and phylogenetic continuity of animal species including humans, and the eminently practical observation that when both kinds of data exist they generally agree, at least in qualitative ways important in hazard identification. The principle of extrapolation from appropriately conducted laboratory animal studies to humans is almost universally accepted in the scientific community, except when there are specific data to the contrary.

There are, however, some important exceptions to this principle. Many of the differences relate to the ways various species metabolize a substance (e.g., beta-naphthylamine), to inherent differences in vulnerability of tissues or organs to some agents (e.g., mouse liver tumors), or to unique physiologic structures or mechanisms (e.g., humans have no forestomach).

The DHHS has made a considerable investment in the use of laboratory animals to identify and understand hazardous properties of substances and to apply such information to the evaluation of health risks. Of all the DHHS units, the NIH performs the largest volume of experimentation with laboratory animals. Most of it has been aimed at understanding the mechanisms of action of toxicants and at teasing apart diverse environmental influences on the expression of diseases and repair of damage.

The FDA, at the National Center for Toxicological Research (NCTR), and to some extent the CDC, at the National Institute for Occupational Safety and Health (NIOSH), also perform many studies using standardized toxicity protocols, supplemented by separate studies of metabolism and mechanisms of action. Toxicity data for FDA-regulated substances are usually generated by the regulated industries. The small fraction of such testing performed by the FDA itself is to fulfill requirements such as quality assurance through replication or to resolve scientific controversies through special study designs.

The National Toxicology Program (NTP) in OASH is deeply involved in toxicity testing, mainly for the identification of carcinogenic properties using the NCI bioassay technique and its derivative designs. The NTP is the focal point not only in the DHHS but throughout the government for carcinogenicity testing and the results of its studies are used by other units as a basis for hazard identification.

By contrast, the missions of many units and subunits concerned with risk assessment require little or no research or testing with laboratory animals to identify hazards. Some examples are the CDC's CHPE and Center for Environmental Health (CEH); the OASH's NCHS, National Center for Health Services Research and Health Care Technology Assessment (NCHSR/HCTA), Committee to Coordinate Environmental and Related Programs (CCERP), and Office on Smoking and Health (OSH); and the the NIH's Recombinant DNA Advisory Committee (RAC), and Office for Protection from Research Risks (OPRR). Each of these, however, may use animal data from other sources in its analyses.

The role of animal data in hazard identification depends on the nature and purpose of the risk determination and on the professional orientation of the group performing the analysis. Within the department, the FDA, the National Institute of Environmental Health Services (NIEHS) and the National Cancer Institute (NCI) in the NIH, the NIOSH and CEH in the CDC, the Agency for Toxic Substances and Disease Registry (ATSDR), and NTP in the OASH all rely extensively, but not exclusively, on laboratory animal investigations to identify hazards that are mostly chemical and physical.

While studies in humans and animals are the primary methods for identifying potentially hazardous substances or conditions, in vitro tests can supplement and occasionally supplant those methods. Data from in vitro systems, such as cultures of mammalian or bacterial cells, may not only provide a qualitative indication of the toxicity of a material (hazard identification) but provide a basis for understanding the nature of interactions between toxicants and cellular molecules that lead to alterations of structure and function (hazard characterization). Such insight into pathologic processes can suggest ways to prevent their development or reverse their progression.

The utilization of in vitro data varies widely among units of the DHHS. The NIH supports extensive research in this area. In vitro tests can be used with widely varying reliability to identify agents that produce somatic mutation, which is highly correlated with initiation of cancer in animals, to study the biotransformation of foreign compounds, such as substances that cause anatomical abnormalities in fetuses, and to study compounds that damage genetic material, such as chromosomes, or damage tissues on physical contact.

Other agencies make substantial use of in vitro tests to set priorities for animal and human studies. The NIH's National Heart, Lung, and Blood Institute (NHLBI) used in vitro studies to demonstrate an abnormal cation movement in red cells of patients with essential hypertension, a step in the expression of that disease. The NTP (OASH), through its Chemical Selection Committee, makes extensive use of in vitro data to identify substances that have a high probability of producing cancer in laboratory rodents, and thus to set priorities for inclusion of candidate substances in the NTP cancer bioassay program. The FDA uses mutagenicity tests of some materials to identify needs for cancer testing. The FDA also uses the results of cell culture studies to determine whether materials proposed for use in surgical implants will damage cells with which they come into contact.

Still another approach to hazard identification used by DHHS agencies is the analysis of chemical structure to determine the likelihood that a compound has some biologic property of interest, such as carcinogenicity. This activity is often referred to as analysis of "structure-activity relationships" (SAR). SAR analyses usually take one of two generic approaches. The first begins with a systematic and quasi-mechanical evaluation of existing knowledge about compounds already investigated, then uses that information to estimate the toxic properties of special chemical moieties in those compounds. Results for specific moieties are integrated to infer the risks of a new compound of known chemical structure but unknown biologic properties. This process is usually performed, at least in part, by computer, and provides very rough quantitative estimates of the likelihood of various toxic effects from the agent under investigation. Data bases for such analyses have been developed for only a few adverse effects, most notably cancer and cytotoxicity, and for metabolism.

The second approach is analysis by experts, usually functioning as a group, to reach qualitative or semiquantitative judgments about the likelihood that certain biologic properties of studied compounds will also pertain to some unstudied compound. Analysts with appropriate expertise can often deal with a wide array of toxic properties and biotransformation. Within the DHHS, the NTP (OASH) makes widespread use of this approach to SAR to determine priorities for testing. The FDA also takes such information into account when it requests that petitioners perform additional toxicity testing to clarify the hazardous properties of regulated substances. Other components of the department, such as the NIOSH (CDC) and the NCI (NIH), also use this approach to SAR, though to a lesser extent than either the NTP (OASH) or the FDA. A recent report of the National Academy of Sciences (NAS) (NRC, 1984) emphasized the role of SAR in the early stages of setting priorities for toxicity testing.

Hazard Characterization

Hazard characterization, like hazard identification, requires the evaluation of data from a range of study types. However, as one proceeds from identification to characterization, combinations of data types become more common, so that analyses usually have greater sophistication and depth. Partly for this reason, in vitro and SAR data have a limited role in hazard characterization.

Both epidemiologic and clinical human studies are often designed to focus on multiple endpoints suggested by leads obtained in hazard identification. For example, retrospective clinical studies first demonstrated the existence of the fetal alcohol syndrome (FAS). The ADAMHA's National Institute on Alcohol Abuse and Alcoholism (NIAAA) then designed and conducted a prospective epidemiologic study to characterize the conditions that foster risk and the interactions of multiple risk factors. Similarly, FDA studies of drugs begin with the identification of hazardous properties and pharmacologic effects in laboratory animals and then explore those characteristics in depth. A structured sequence of human clinical trails, often designated Phase I to Phase IV, develop dose-response relationships for both intended and unintended (toxic) effects, establish therapeutic ratios, and delineate conditions for optimal use. OPRR (NIH) regulations and policies have substantial influence here.

When human data are the focal point of a hazard characterization, the uncertainties of interspecies extrapolation are avoided, and the uncertainties of low-dose extrapolation may also be minimized. When the NIMH (ADAMHA) used human clinical studies to evaluate the effects of lithium at therapeutic dose levels, that evaluation was used at a consensus development conference to judge the risks and benefits of the treatment. The NCHSR/HCTA (OASH) has used human data to characterize the risks of new diagnostic tools such as nuclear magnetic resonance (NMR) imaging, existing treatments such as apheresis for the treatment of Goodpasture's Syndrome, and lack of treatment in a decision not to recommend liver transplant. The FDA's Center for Devices and Radiological Health (CDRH) also assessed the risks of NMR imaging and concluded that the information was insufficient to characterize the potential risks of exposure; the FDA subsequently issued a general guideline on the matter, approved the premarketing applications of several manufacturers and assumed responsibility for characterization of the potential safety or risk of exposure to NMR.

Although the use of clinical studies circumvents interspecies and low-dose extrapolations, new uncertainties arise. One kind of uncertainty is whether and how to generalize results from one population group to another that may differ in race or ethnic origin, exposure routes, cultural habits, age, or health conditions; such characteristics may influence risk and alter outcomes. It is, for example, difficult to establish the applicability of data on survivors of the atomic bombs in Japan in determining the probability that mammography screening will cause breast cancer in women in the United States, because background incidence patterns for breast cancer differ markedly in the two countries.

Hazard characterization usually requires some estimate of the dose-response relationships for the various adverse effects of the substance under review. Toxicity studies in animals generally include reliable quantitative data on exposure, while reliable human exposure data are often lacking for even the most sophisticated epidemiologic investigations. Consequently, dose-response relationships must usually be estimated from studies in animals. Three problems immediately arise: (1) animals must often be exposed at doses much higher than those that have affected, or are likely to affect, humans, so that effects at low doses must be predicted using theories about the form of dose-response relationships; (2) animals and humans often differ in susceptibility; and (3) the human population is far more heterogeneous than the test species, so that some individuals are likely to be substantially more susceptible than the average. Hazard characterization includes attempts to address these issues.

The level of mathematical treatment in hazard characterization differs from one risk assessment to another because of differences in the type, quality, and quantity of biological information as well as basic understandings about disease mechanisms. Such disparities are particularly apparent when pivotal information is derived from laboratory animals exposed to doses much higher than those encountered in the human condition. Illustrations are the testing of pentachloroethane for carcinogenicity by the NTP (OASH) and the reproductive toxicity testing of 2,3,7,8,-TCDD (dioxin) by the NIEHS (NIH). Because mathematical modeling of dose-response curves for carcinogens is widely accepted as a valid tool for estimating human risks at low doses (though there is presently no way to estimate the precision or accuracy of these models), the positive results for pentachloroethane can be tested by models such as the multistage model to derive risk estimates. By contrast, no such models are in use for reproductive toxicity. Hence, adverse reproductive effects of dioxin are reflected in standards for human exposure that are based on safety factors.

The nature and depth of hazard characterization depend to some degree on the anticipated extent and duration of exposure. If the exposure is expected to be large and widespread, as in the contamination of the food supply with ethylenedibromide (EDB), then the need for hazard characterization is correspondingly large.

Human and laboratory animal data for noncancer toxicity are evaluated with the same rigor as those for cancer, though the information is then used in somewhat different ways. The major differences are related to assumptions that (1) thresholds exist for most noncancer effects, although no one knows as yet how to measure or identify thresholds in a large heterogeneous population; (2) the results of laboratory animal studies, especially the no-observed-effect level (NOEL) may somehow be directly translated into a usable lower bound on individual human thresholds; and (3) humans must be protected even when the overall risk of the hazard under study may be substantially affected by prior, concurrent, or later exposures to other agents. For example, the FDA's Center for Food Safety and Applied Nutrition (CFSAN) requires the sponsor of a food additive or color additive to conduct appropriate toxicology testing to evaluate the health hazards of the additive, and to estimate its expected use. These substances are regulated on the basis of acceptable daily intake (ADI) levels calculated from NOELs, and the ADIs are designed to be uniformly applicable so that exceptions are not needed for sensitive subgroups or for persons with other exposures.

Designs for toxicity studies using laboratory animals such as rats and mice also vary widely because of the need to accommodate different and sometimes incompatible objectives. Studies of carcinogenic effects and certain reproductive effects may both involve lifetime feeding of some toxic agent, but they may require different strains of rodents, different dosage regimens, and different holding conditions. Regulatory and public agencies have developed relatively well standardized tests for some types of toxicity—cancer, birth deformities, reproductive dysfunction, chronic toxicity, and acute mortality—in connection with the premarket testing requirements imposed on certain classes of chemicals, but many other tests and research-oriented investigations use specialized study designs. Many protocols, standardized and specialized, require two or more "tests" in sequence. A carcinogenicity test often begins with a single-dose acute study. This is followed by a 14- to 28-day study to determine dose ranges, then by subchronic studies to determine sites of toxic damage to refine dose schedules. Only after three preliminary studies is the main two-year study begun.

In addition, though mechanistic and toxicokinetic studies are not always available, they can provide a valuable—and sometimes critical—supplement to data from conventional toxicity tests. The NIH conducts many such studies to enhance insight into how substances cause toxic effects and to determine the extent to which laboratory animal models are concordant with human responses. Mechanistic studies have been performed to characterize risk factors from lifestyles, such as dietary fat and cancer, and toxicokinetic studies were useful in understanding analgesic-associated kidney disease. Such data help to define the levels of certainty that underlie statements about human risks.

Exposure Characterization

Exposure characterization focuses (1) on the number and characteristics of people exposed, and (2) the specific conditions and degrees of those exposures. The characterization may be conducted at various levels of specificity and detail.

Some DHHS units are principally concerned with defining the population exposed to a risk factor, whereas others focus on elucidating the characteristics of exposure that are associated with pathological responses. The former often reach conclusions that qualitatively describe a population considered at risk, but may not estimate in detail the size and characteristics of that population. Examples are the OSH (OASH) exposure characterization for passive smoking and the ATSDR exposure characterization for hazardous wastes. The absence of quantitation of exposure may be due to the paucity of data, as in the case of analgesic-associated kidney disease. In other circumstances, the size but not the characteristics of the population at risk may be estimated, as in the NIOSH's (CDC) listing of the number of people working in each occupation with potential exposure to EDB.

Exposure characterization is not limited to populations currently at risk, but may extend to the past (to identify populations for research on delayed effects, or to provide monitoring and surveillance to minimize those effects) or to the future (to identify populations that will benefit from the control of potential risk). For example, the NCHSR/HCTA (OASH) has characterized the populations that would benefit and be at risk from transplantation of the liver and percutaneous transluminal coronary angioplasty (PTCA).

Sophisticated data collection and analytic tools may be used to characterize exposure. The national data collection efforts of the NCHS provide some of the most commonly used exposure data used by DHHS health units in making determinations of risk. The NCHS (OASH) is authorized to use its capabilities for national data systems and demographic analyses to collect profiles of exposure to toxic agents, and the National Health and Nutrition Examination Survey (NHANES) provides physiologic exposure indicators for a variety potential health risks. In the NHANES II, the NCHS measured blood lead levels in the general U.S. population, and the data were analyzed for time trends and for associations with selected demographic and socioeconomic factors.

Other exposure measurements used by DHHS units include estimates of exposure of high-risk groups to suspect carcinogens, used by the NCI (NIH) in planning epidemiology studies; biologic monitoring of high-risk groups by the CEH (CDC), such as body burden of PCBs in populations near waste dumps; risk factor exposure and disease surveillance systems, by the CHPE (CDC); and exposure profiles in Health Hazard Evaluations (HHEs) of workers and workplaces by the NIOSH (CDC). The CEH's Clinical Chemistry Division is a major focus for direct measurement of exposure to hazardous materials.

Characterization of the prevalence of a hazard is the focus of some units. The NIDA (ADAMHA) uses specifically contracted studies to determine the prevalence of drug abuse and at the same time identifies high-risk populations. On occasion, commercial polling survey companies will provide risk prevalence data which will prove of interest to one or another DHHS unit seeking to estimate exposure levels.

Risk Determination

The essential feature of risk determination is synthesis: it is in this step that the first three steps of the risk assessment process are brought together and integrated to reach a broad conclusion (qualitative or quantitative) about the degree of risk associated with some defined exposure. Not all DHHS units involved in one or another of the component stages of risk assessment actually perform risk determinations. The FDA conducts complete risk determinations as necessary background information for its regulation of food substances, drugs, cosmetics, and radiation-emitting productivity and devices. By contrast, the NTP (OASH) does not make risk determinations, although NTP technical reports are often used by other DHHS units in their own risk determinations.

The products of risk determinations range from relatively simple qualitative statements of risk to highly detailed sets of complex mathematical estimates. The NIDA (ADAMHA) concluded, without quantitation, that marijuana causes acute and chronic health effects and noted pulmonary and reproductive changes among the prevalent effects. Similarly, the NCI (NIH) has made the qualitative determination for public information purposes that diets low in fiber cause increased risk for certain types of cancer. On the other hand, the CEH (CDC) determined a specific, numeric "level of concern" for 2,3,7,8-TCDD in residential soil, with detailed numeric estimates of increases in cancer risk.

Some units of DHHS perform risk/benefit analyses (RBAs) as part of the risk determination step. The NCHSR/HCTA (OASH) and the NIMH (ADAMHA) performed RBAs in the course of their assessments of the use of PTCA and of lithium treatment of patients with mood disorders, respectively.

Within DHHS, several kinds of approaches are used to perform risk determinations, including the appointment of external groups and requests to standing or ad hoc internal groups. The NIH often uses external sources such as consensus development conferences to assess and integrate the information from hazard identification, hazard characterization, and exposure characterization. One example is the use of a consensus conference by the NHLBI (NIH) to reach a determination on the nature and extent of risk of elevated blood cholesterol levels for heart disease.

A similar format is used by other units. The FDA turns to its

Cancer Assessment Committee for guidance, and to the Food Additive Safety Evaluation Branch (FASEB) for review panels to consider the safety of food chemicals; and the CDC relied on the Advisory Committee on Immunization Practices (ACIP) to estimate the health risks of swine flu. The OASH asked the CCERP to assess the risks of exposure to EDB. In some instances, perhaps most often where the data are clearcut and straightforward and where conclusions are likely to be noncontroversial, this synthesis is performed internally by one or several professional staff members of the DHHS unit.

As pointed out earlier in this section, different units of DHHS base their risk determinations on different kinds of pivotal information; some rely on epidemiologic studies while others place emphasis on whole animal studies. The NIOSH (CDC), for example, seeks to base each criteria document on epidemiologic evidence about possible adverse effects of a substance. When such data are absent or judged to be inadequate for reliable risk judgments, it uses animal studies that mimic known routes and extents of human exposure or provide insight into the absorption, excretion, and metabolism of the subtances. The FDA relies almost entirely on animal studies to identify potential human hazards of direct food additives (e.g., antioxidants and artificial sweeteners), animal feed additives (e.g., growth promoters), and cosmetics (e.g., colors such as D&C Green No. 6). This is in sharp contrast to FDA's predominant reliance on data from humans (but with supporting information from laboratory animals) for approval of prescription drugs. The CDC bases its assessment of infectious risks primarily on information from humans, as illustrated by its analyses of immunization against swine flu and pertussis.

Regardless of the weights given to various types of supportive data, in each case the step of determining risk is an integrative one. Whether involving the application of a mathematical model to data generated from studies specifically designed for use in a risk assessment, or the development of a consensus among panel members reviewing a wide range of data from investigator-initiated research, determining risk requires integrating the information available from work relevant to a particular hazard's identification, its characterization and the magnitude of the exposure. This sort of synthesis is characteristic of the effort whether it is formal or informal, whether it is undertaken in anticipatory actions that are regulatory, or those that are advisory, or those that are service-oriented. On the other hand, the method chosen to make a determination of risk often has substantial implications for risk management. For example, if a quantitative determination is made, the precise determination of exposure levels becomes more compelling for intervention purposes. If a panel of scientific experts is involved in the determination process, whether qualitative or quantitative, the choice of panel members can shape the nature of the outcome. A variety of factors influence the way risk determinations are made. Some relate to the available data, some relate to the nature of the hazard under consideration, some relate to the risk management options available, and some to individual agency mandates or procedures. Understanding the way those factors work is important to identifying ways to improve DHHS efforts to make determinations of risk.

FACTORS INFLUENCING DISTINCTIONS IN APPROACH

Exhibit 9–1 notes variations across the 30 case studies examined in Chapters 4 through 8 by (1) the sponsoring agency, (2) the source of the risk being assessed, (3) the purpose of the assessment, (4) the risk assessment steps undertaken, (5) the types of information available, and (6) the form of the resulting expression of risk. Exhibit 9–2 provides a more detailed legend for the axes used in Exhibit 9–1. These 30 cases are meant to provide only a glimpse of the activities undertaken by the units. While they capture the essential variety of DHHS risk assessment activities, they are not meant to be fully representative of the range of each unit's activities.

The sources of health risks addressed by the DHHS (Exhibit 9–1, column 3) can be broadly categorized into five types—those genetically determined (inborn), those consciously selected (behavioral), and those that result from exposure to exogenous microbiological, chemical, and physical agents—but often more than one of these categories contributes to the existence of a single health risk.

Within the department, risks are determined in anticipation of numerous risk management options (see Exhibit 9–1, column 4). Much attention is directed at identifying risks to provide guidance to professionals engaged in diagnosing the cause of diseases and in protecting the health of the general population, and to direct the attention of the public at large to health concerns important for lifestyle decisions. In many cases, risks are ascertained in order to make public health decisions under regulatory mandates. When regulations are challenged in the courts, the agency must be fully prepared to present a careful and systematic analysis of the health risk information that was used as the basis for judgments.

Exhibit 9–1 Characteristics of DHHS Health Risk Determination Cases*

Cases	*Agency*	*Source of Risk*	*Purpose of Risk Assessment*[1]	*Components of Risk Assessment*	*Types of Information Used*[2]	*Expression of Risk Determination*
Schizophrenia	ADAMHA	inborn	Prof ed	1,2,3,4	*epi*, *clin*	qual-panel
Lithium	ADAMHA	chemical	Prof ed	1,2,3,4	*clin*	risk-ben
Fetal Alcohol Syndrome	ADAMHA	behavioral-chemical	*Public ed*/Prof ed	1,2,3,4	*epi*, *clin*, animal	qual-panel
Phencyclidine	ADAMHA	behavioral-chemical	Public ed	1,2,3,4	*clin*	qual-informal
Marijuana	ADAMHA	behavioral-chemical	Public ed	1,2,3,4	*animal*, clin	qual-informal
Dioxin in soil	CDC	chemical	Reg-corr	1,2,3,4	*animal*, epi	math-unit
Aspirin-Reye Syndrome	CDC	chemical	*Public ed*/Prof ed/Reg-corr	1,2,3,4	*epi*	qual-panel
Toxic Shock	CDC	behavioral-microbial	Reg-corr	1,2,3,4	*epi*	qual-informal
Swine flu	CDC	microbial	*Public ed*/Serv prog	1,2,3,4	*epi*, pharm/met	qual-panel
Pertussis	CDC	microbial	Serv prog/*Prof ed*	*1,2,4*	*epi*	risk-ben
Ethylene dibromide	CDC	chemical	Reg-corr	1,2,3,4	*animal*, in vitro	math-unit
Ethylene dibromide	OASH	chemical	Reg-corr	2,3,4	*animal*, in vitro	qual-panel
Styrene	CDC	chemical	Reg-corr	1,2,3,4	*animal*, epi	math-sf
Grain/feed mills	CDC	physical	Reg-corr	1,2,3,4	*epi*	inter-risk
D&C Green No. 6	FDA	behavioral-chemical	Reg-corr	1,2,3,4	*animal*	math-unit
6-Methylcoumarin	FDA	chemical	*Reg-corr*/Prof ed	1,2,3	*clin*, epi	N/A
Diethylstilbestrol (DES)	FDA	chemical	Reg-corr	1,2,3,4	*animal*, epi	math-unit
Moxalactam	FDA	chemical	Reg-corr	1,2,3,4	*clin*, pharm/met, epi	qual-panel
Orthopedic Implants	FDA	physical-chemical	Reg-preemp	1,2,3,4	*clin*, animal	inter-risk
Fat & Cancer	NIH	behavioral-chemical	Public ed	1,2,3,4	*epi*, clin, animal	qual-panel
Fat & Heart Disease	NIH	behavioral-chemical	Public ed	1,2,3,4	*clin*, epi, animal	qual-panel
Radio-epi Tables	NIH	physical	Litigation	1,2	*epi*	N/A
Cloning-Shiga	NIH	microbial	Reg-preemp	1,2,3,4	*in vitro*, clin	risk-ben/safety factor
Mammography	NIH	physical	Prof ed	1,2,3,4	*epi*, animal	qual-panel
Analgesic-Kidney Disease	NIH	chemical	Prof ed	1,2,4	*epi*, animal	qual-panel

Exhibit 9–1 (continued)

Cases	*Agency*	*Source of Risk*	*Purpose of Risk Assessment*[1]	*Components of Risk Assessment*	*Types of Information Used*[2]	*Expression of Risk Determination*
Liver transplant	OASH	physical	*Serv prog*/Prof ed	1,2,3,4	*epi*, clin	risk-ben
Percutaneous transluminal coronary angioplasty	OASH	physical	*Serv prog*/Prof ed	1,2,3,4	*epi*	risk-ben
Lead exposure	OASH	chemical	Reg-corr	3	*epi*	N/A
Pentachloroethane	OASH	chemical	Reg-corr	1,2	*animal*	N/A
Passive smoking	OASH	behavioral-chemical	Public ed	1,2,3,4	*epi*, clin	qual-informal

*See Table 9–2 for an explanation of column categories and abbreviations.

[1] Italics indicate the primary purpose of the assessment.

[2] Italics indicate the primary information relied upon.

Abbreviations: ADAMHA = Alcohol, Drug Abuse, and Mental Health Administration; CDC = Centers for Disease Control; OASH = Office of the Assistant Secretary for Health; FDA = Food and Drug Administration; NIH = National Institutes of Health.

Exhibit 9–2 Categories of Information for Axes in Exhibit 9–1

Category 1: Source of Risk

- Inborn
- Behavioral
- Microbial
- Chemical
- Physical (radiation/trauma)

Category 2: Purpose of Risk Assessment (*primary* vs. secondary)

Public advisory/education	(Public ed)
Professional education	(Prof ed)
Service program decision	(Serv prog)
Regulatory—pre-emptive	(Reg-preemp)
Regulatory—corrective	(Reg-corr)
Litigation	(Litigation)

Category 3: Components of Risk Assessment

1. Hazard identification
2. Hazard characterization
3. Exposure characterization
4. Risk determination

Category 4: Types of Information Used (*pivotal* vs. supporting)

Human clinical trials	(clin)
Epidemiologic studies	(epi)
Whole animal studies	(animal)
In vitro studies	(in vitro)
Pharmacokinetic/mechanisms	(pharm/met)

Category 5: Expression of Risk Determination

Mathematical—safety factor	(math-sf)
Mathematical—unit risk	(math-unit)
Formal decision analysis	(formal)
Inter-risk comparison	(inter-risk)
Qualitative—panel reviews	(qual-panel)
Qualitative—informal scientific advice	(qual-informal)
Risk-benefit analysis	(risk-ben)

Although risk determinations encompass all relevant data about the cause of health damage, inferences about the nature and magnitude of the risks often depend largely on one, or at most a few, key studies of one or another of the five information types (Exhibit 9–1, column 6) presented initially in Exhibit 2–2. The analytic tools applied to these data types are determined by the nature of the data base available, the agency involved, and the risk management decision required. The weight given to the various components of the hierarchy of data used in risk assessments generally decreases from human clinical trials, to epidemiology, animal studies, in vitro studies, and theory (SAR), in that order. Studies of pharmacokinetics and mechanisms may cut across and support any or all of these. In some instances human studies lack characteristics important to risk determination (e.g., dose-response information) and hence results from animals studies may take on greater importance in the risk assessment.

Results of risk determinations are presented in different forms (Exhibit 9–2, category 5). Some forms are based on mathematical analysis, some are highly subjective, and still others compare and contrast important—though often disparate—elements or risk assessment and management. In the following review of how various factors influence the nature of the analysis in risk assessment, the axes of presentation are drawn from the categories in Exhibit 9–1—(1) source of risk and type of adverse effect; (2) information type in relation to uses of risk assessments; (3) information types in relation to form of risk conclusions; and (4) form of risk assessment conclusion and nature of health effect.

Source of Risk and Type of Adverse Effect

The reasons for health risk assessment activities by DHHS agencies are broad and diverse but may be grouped into two general categories, one deriving from effects and one from exposures: the need to identify sources of increased health risks, given observable adverse health effects; and the need to identify the effects of some possible health risk, given that it is already present in society, or to estimate the effects if some change is introduced in society. One begins with a possible cause and looks for effects; the other begins with observed effects and looks for a cause. Either of these can be the stimulus for further work that culminates in a risk assessment, and both approaches are common in the DHHS. Exhibit 9–1 shows that the 30 case studies deal with a wide variety of health effects, as well as a wide variety of potential risks. Studies of possible cause-effect relations must focus on both a set of input variables (here, exposures, perhaps in combination with demographic features and other risk factors) and one or more output variables (here, mostly measures of morbidity and mortality). Among the agencies stimulated by an appreciation of the need to understand and control a specific disease, the CDC initiated human and laboratory animal studies to define the conditions that lead to toxic shock syndrome and influence its severity; the FDA continually surveys the toxicologic literature to identify previously unforeseen adverse effects and unanticipated toxic potentials of drugs, cosmetics, and substances in foods; and the ADAMHA seeks to identify environmental conditions that impair mental health. At the NIH, the National Institute on Dental Research (NIDR) seeks to identify and estimate the relative contribution or risk factors associated with the causes, prevention, diagnosis, and treatment of oral diseases; and the National Institute of Neurological and Communication Disorders and Stroke (NINCDS) conducts prospective studies of elderly persons to identify, and in part quantify, the role of prior heart disease, hypertension, age, race, and lifestyle as risk factors for stroke.

The results of such work provide improved bases for health promotion and disease prevention. Thus, the identification of DES as a cause of vaginal cancer in young women has helped to limit its use as a therapeutic agent and as an additive to animal feed; the knowledge that cigarette smoking increases the risk of numerous medical conditions has stimulated attempts to change cultural patterns in smoking and to modify the contents of cigarette smoke via filtration and compositional changes; and the understanding of the prevalence and impact of mental disorders has stimulated neurochemical research to obtain pharmacologic agents effective in the treatment of schizophrenia.

In the opposite approach, initial concern is motivated by potentially hazardous exposures rather than the observation of effects. All units of the DHHS are sensitive to the need to identify health risks of materials proposed for introduction into society; and all units perform some type of prospective risk assessment before the substance, treatment, experiment, or other potential health risk is put into use. The regulatory compliance activities of the FDA cause it to engage in this function more extensively than any other DHHS unit. The FDA conducts risk assessments during premarket approval for new food colors and additives, cosmetics, human and animal drugs, and diagnostic and therapeutic devices, as, for example, in the assessment of both safety and effectiveness during the premarket review process for orthopedic implants.

Among the other units involved in a risk assessments motivated by exposure, rather than outcome, the OPRR (NIH) has the primary responsibility of ensuring that, for all research funded by the DHHS, any expected risks to human subjects are outweighed by the expected benefits of the research. A number of other agencies have performed assessments initially motivated by exposure to a known or potential hazard:

- The NIH established the RAC to assess potential risks of recombinant DNA technology when concerns surfaced about possible hazards from genetically engineered life forms. This committee was then asked to review and approve cloning in *E. coli* K-12 of the structural gene of the Shiga-like toxin found in *E. coli.*
- The NCHSR/HCTA (OASH) conducted an extensive assessment to balance the risks associated with performing liver transplants against those of not performing that operation.
- The NCHSR/HCTA (OASH) evaluated the risks of using percutaneous transluminal coronary angioplasty as an alternative to the more established form of treatment, coronary bypass operation.
- The CID (CDC) reviewed the scientific evidence that emergence of the swine flu virus presented a significant risk of an influenza pandemic and that a nationwide immunization program was needed.

All of these hazards except the first were in fact present to some degree at the time the risk assessment was initiated. This tends to be the rule for many risks subjected to assessment in the DHHS due to a variety of factors, such as (1) earlier reliance on insensitive studies that did not detect or adequately characterize certain effects; (2) new uses of a substance leading to different effects and different risks than had been studied previously; (3) increased public sensitivity to risks that were once considered acceptable; or (4) a delay in recognizing that some hazard was likely to be widely distributed and to need prompt risk assessment. To cite a few examples, marijuana has been used for centuries, but scientists at the NIDA (ADAMHA) and elsewhere are only beginning to understand its long-term, possibly permanent effects on both mind and body. The NIEHS continues its explorations of the toxic properties of inhaled paraquat, a registered herbicide that is used to destroy growing marijuana fields, but may find its way into drugs of abuse made from the harvested contaminated crop. Finally, liver transplants had been done over a period of years, but only rarely; recently the procedure developed to a point where a risk assessment was both feasible and necessary.

Information Types in Relation to Uses of Risk Determinations

Exhibit 9–2 (category 2) presents six potential uses of risk determinations: public advisory or education, professional education, service program decision, regulatory preemptive action, regulatory corrective action, or litigation. Exhibit 9–3 juxtaposes these uses

Exhibit 9–3 Primary Information Relied Upon in Making Risk Determinations for Each Case Study Based on Anticipated Use of the Risk Determinations*

Cases	*Advisory/Education*	*Professional Education*	*Service Program Decision*	*Regulatory Pre-Emptive*	*Regulatory Corrective*	*Litigation*
Schizophrenia		*epi*, *clin*				
Lithium		*clin*				
Fetal Alcohol Syndrome	*epi*, *clin*, animal	*epi*, *clin*, animal				
Phencyclidine	*clin*					
Marijuana	*animal*, clin					
Dioxin in soil					*animal*, epi	
Aspirin-Reye Syndrome	*epi*	*epi*			*epi*	
Toxic Shock					*epi*	
Swine flu	*epi*, pharm/met		*epi*, pharm/met			
Pertussis		*epi*	*epi*			
Ethylene dibromide					*animal*, in vitro	
Styrene					*animal*, epi	
Grain/feed mill					*epi*	
D&C Green No. 6					*animal*	
6 Methylcoumarin		*clin*, epi			*clin*, epi	
Diethylstilbestrol (DES)					*animal*, epi	
Moxalactam					*clin*, pharm/met, epi	
Orthopedic Implants				*clin*, animal		
Fat & Cancer	*epi*, clin, animal					
Fat & Heart Disease	*clin*, epi, animal					
Radio-epi Tables						*epi*
Cloning-Shiga				*in vitro*, clin		
Mammography		*epi*, animal				

Exhibit 9–3 (continued)

Cases	*Advisory/Education*	*Professional Education*	*Service Program Decision*	*Regulatory Pre-Emptive*	*Regulatory Corrective*	*Litigation*
Analgesic Kidney Disease		*epi*, animal				
Liver transplant		*epi*, clin	*epi*, clin			
Percutaneous transluminal coronary angioplasty		*epi*	*epi*			
Lead					*epi*	
Pentachloroethane					*animal*	
Ethylene dibromide					*animal*, *in vitro*	
Passive smoking	*epi*, clin					

*Italics indicate the primary information relied upon. See Exhibit 9–2 for an explanation of column abbreviations.

with cases and indicates the types of information used to reach risk conclusions in case studies. Animal data tend to dominate the risk assessments for regulatory purposes, human data for all other purposes, but no risks except those of D&C Green No. 6 and ethylene dibromide were determined exclusively by the use of whole animal toxicity studies. In only a few cases was additional information available about the metabolism of the substance and about the means—at the molecular level—by which it alters normal bodily function and injures organs.

There appears to be a set of complex interactions between the types of information available and use of the resulting risk assessment. If limits on data type, strength, and relevance limit confidence in the risk assessment, strong actions, including regulation, are not appropriate. Conversely, perceived needs to take action may stimulate the development of data for use in future risk assessments. These interactions are evident in many of the case studies, and are particularly clear when a risk assessment includes a recommendation for additional research on specific, relevant topics.

All DHHS agencies are concerned about information types, the uses of their risk assessments, and the relations between the two. The great scope and depth of hazard identification efforts at the NIEHS, for example, is documented in the long-term research agenda for that institute. The NIEHS explores compounds to which humans are exposed by all routes, including atmospheric pollutants such as carbon monoxide and nitrogen oxides, workplace carcinogens and reproductive toxicants, natural plant toxins and metals that contaminate foods, chlorinated organics in drinking water, and special environmental problems associated with home and neighborhood.

Likewise, the FDA performs, often at its NCTR, specialized toxicological investigations on selected food additives, dietary contaminants, natural foodstuffs, animal drugs, and pharmaceuticals. The FDA also continually assesses reports on the health effects of substances already approved for use. This postmarket surveillance may lead to a reassessment of risks, if there is convincing evidence that the substance has effects not anticipated from earlier studies or that known risks are more frequent or more severe than was expected. Postmarket surveillance of moxalactam disodium by the FDA's Center for Drugs and Biologics (CDB) revealed a much higher risk of moxalactam-induced interference with blood coagulation than had been expected from clinical trials. In other cases, new analytic methods are being used to measure toxicants at concentrations previously undetectable; for example, FDA approval of DES in animal feeds and implants was based on analytical methods used in the 1950s, but newer methods available in the 1960s and 1970s could detect much lower levels of DES. Because this increased sensitivity of detection allowed stricter regulatory control than was feasible in earlier years, a new assessment of potential health risks at exposure levels that once had no regulatory implications became necessary.

The CDC has participated actively in this type of hazard evaluation in (1) an investigation (for the state of New York and the federal EPA) of possible chromosomal abnormalities among residents of the Love Canal area who were exposed to hazardous wastes; (2) epidemiologic surveillance of individuals exposed to milk contaminated with the flame retardant polybrominated biphenyl (PBB); and (3) exhaustive investigations into the environmental causes or correlates of both Legionnaire's Disease and TSS.

The NIH performs retrospective risk assessments as illustrated by the formulation of radio-epidemiological tables to estimate the likelihood of cancer in individuals who have been exposed to radiation therapeutically, occupationally, or accidentally. Similarly, the risks of using mammography as a screening method, rather than a diagnostic tool, were assessed by the NIH when concern was raised that changes in use might lead to alterations in risk profiles.

As noted above, the data relied upon most frequently are those obtained in human studies. Human studies are either epidemiologic or clinical; however, the former are more frequently available than clinical studies, because population studies often have higher sensitivity associated with large numbers of subjects and do not raise the same ethical concerns as are common with clinical investigations. In all cases, the human evidence is buttressed by data from laboratory animals.

Information Types in Relation to Form of Expression of Risk Conclusion

A statement of risk conclusions may be expressed in any of at least seven types of forms (Exhibit 9–2, category 5). The differences in use for each form of expression used in the case studies are noted in Exhibit 9–4.

Units of the DHHS often attempt to estimate, for both prospective and retrospective risk determinations, the likelihood that health effects might in fact occur (Exhibit 9–4). Many of these numeric estimates are for the risks of known or suspected carcinogens, and they are derived most often from studies of laboratory

Exhibit 9–4 Expression of Risk Conclusions for Case Studies Depending Upon the Information Pivital to the Risk Determination*

Cases	*Human Clinical Studies*	*Epidemiologic Studies*	*Whole Animal Studies*	*In Vitro Studies*	*Pharmacokinetico Mechanism*
Schizophrenia	qual-panel	qual-panel			
Lithium	risk-ben				
Fetal Alcohol Syndrome	qual-panel	qual-panel	qual-panel		
Phencyclidine	qual-informal				
Marijuana	qual-informal		qual-informal		
Dioxin in soil		math-unit	math-unit		
Aspirin-Reye Syndrome		qual-panel			
Toxic Shock		qual-informal			
Swine flu		qual-panel			qual-panel
Pertussis		risk-ben			
Ethylene dibromide			math-unit	math-unit	
Styrene		math-safe fac	math-sf		
Grain/feed mills		inter-risk			
D&C Green No. 6			math-unit		
6-Methylcoumarin	N/A	N/A			
Diethylstilbestrol (DES)		math-unit	math-unit		
Moxalactam	qual-panel	qual-panel			qual-panel
Orthopedic Implants	inter-risk		inter-risk		
Fat & Cancer	qual-panel	qual-panel	qual-panel		
Fat & Heart Disease	qual-panel	qual-panel	qual-panel		
Radio-epi Tables		N/A			
Cloning-Shiga	risk-ben/math-sf			risk-ben/math-sf	
Mammography		qual-panel	qual-panel		
Analgesic-Kidney Disease		qual-panel	qual-panel		

Exhibit 9–4 (continued)

Cases	*Human Clinical Studies*	*Epidemiologic Studies*	*Whole Animal Studies*	*In Vitro Studies*	*Pharmacokinetico Mechanism*
Liver Transplant	risk-ben	risk-ben			
Percutaneous transluminal coronary angioplasty		risk-ben			
Lead exposure		N/A			
Pentachloroethane			N/A		
Ethylene dibromide			qual-panel	qual-panel	
Passive smoking	qual-informal	qual-informal			

*See Exhibit 9–2 for an explanation of column abbreviations.

animals. Numerical statements are sometimes generated for noncarcinogens to indicate subjectively the relative likelihood of the absence of risk. Such values are not commonly presented as probability analyses or probability statements themselves about the possible occurrence or absence of adverse consequences, though Bayesian probabilities might be used for such purposes.

Whether the conclusion of a risk assessment is expressed in quantitative terms is not demonstrably related to the extent of reliance on human data (Exhibit 9–4). A few case studies reached risk-benefit conclusions using clinical data: these represent relatively unusual circumstances in which risk and benefits are commensurable entities subject to objective measurement that could be weighed against one another during the phase of risk assessment. In most situations, risk-benefit comparisons are within the domain of risk management rather than risk assessment because benefits accrue primarily to parts of the society other than those confronted with the corresponding health risks.

The most substantial implication of the various forms in which a risk determination is expressed is related not to the validity of the determination, but to how the determination is to be used and interpreted by a decision maker. Such variety requires that any determination forwarded for a risk management decision be accompanied by a carefully developed summary of the process by which the determination was reached, the type of expertise involved and level of consensus, the nature and quality of the data, and the principal sources of uncertainty.

Form of Risk Assessment Conclusion and Nature of Health Effect

Risk estimates for carcinogens are commonly derived from extrapolations of high-dose experimental data, at times in combination with epidemiologic data, and rely on mathematical models that imply various assumptions about relevant biologic and pathologic processes. For example, the NIOSH (CDC) estimated the risks of exposure to EDB by application of the multihit and multistage models to the data from two animal studies, as the foundation of recommendations for standards to protect the health of EDB workers. Similarly, the NIOSH (CDC) publishes criteria documents, of which some, like the one on styrene, recommend an occupational standard; the CEH (CDC) not only estimated the level of risk for exposures to soils contaminated with dioxin but also recommended that levels of dioxin in residential soil above a specific “level of concern” should be regarded as possibly presenting significant risk to human health; and the CCERP (OASH) reviewed various quantitative risk assessments of EDB and the corresponding risk estimates that had been generated throughout the government. Prominent exceptions of course exist, as in the use of epidemiologic data by the 1964 surgeon general's panel on the relation between cancer and cigarette smoking and the more recent NCI work on dietary factors in cancer.

Some units are required by law to quantify their estimates of risk; sometimes the methods of quantitation are also specified by regulation. Public Law 97-414 directs the secretary of the DHHS to devise and publish radio-epidemiological tables that estimate the likelihood that a cancer found in a specific person was associated with a specific radiation exposure at some earlier time. By contrast, the Food, Drug, and Cosmetics Act specifies neither the need for quantified estimates of risk nor the methods of deriving risk estimates; however, the FDA's proposed regulation on "sensitivity of the method" specifies that the FDA will use a linear model for extrapolating high-dose animal data to estimate risks. The resultant estimate will be compared to norms of risk acceptability to establish the permitted human exposure from the edible products of animals treated with a carcinogenic animal drug.

Numeric values for noncarcinogens are usually statements of a "safe dose," based on the concept of thresholds and determined by dividing an experimental NOEL by one or more safety factors. The choice of safety factor used may depend on the availability of various kinds of human and animal toxicity data, the uncertainty associated with the data, and the nature of the effect. For example, safety factors for cancer are often larger than safety factors for other endpoints.

Such nonprobabilistic quantitation is common at the CDC, FDA, and NIH, which rely more extensively on epidemiologic data providing comparative estimates for various risk groups. Examples include the CDC's efforts to assess the health risks of the pertussis vaccine (because use of the vaccine has led to CNS ailments in some children, while nonuse of the vaccine can result in pertussis; both are observable adverse health effects) and the risks of using aspirin for treatment of viral illnesses in children (because of the possible association between Reye Syndrome and aspirin use); and the FDA's efforts to derive estimates of safe concentrations of contaminants in, and direct additives to, the human diet. For noncarcinogenic substances other than drugs, the FDA may select one of two similar approaches: either the application of a predetermined safety factor to the NOEL to arrive at an ADI, or the determination of a margin-of-safety (MOS) by dividing the NOEL by the anticipated or known human exposure to determine whether an exposure is allowable. In the latter approach, a qualitative judgment must be reached about the suitability of the magnitude of each MOS.

CROSS-CUTTING ISSUES

Other issues may also serve as a basis for study of health risk assessment activities within the DHHS—setting priorities, data needs, staff needs, organizational placement, and scientific review.

Setting Priorities

Deciding which risks or possible risks will be the subject of a risk assessment and deciding when to undertake an assessment are determined sometimes by statutory mandates and sometimes by nonstatutory considerations. FDA risk assessments for food additives and drugs are governed in part by statute, and the statutory language sometimes prescribes—with little flexibility—priorities and criteria for performing risk determinations. Thus, the FDA must act within 180 days on a New Animal Drug Application (NADA), or on a petition to the Division of Food and Color Additives for approval of a new food additive or color additive for either foods or cosmetics; and it must respond within 30 days after submission of an Investigative New Drug (IND) application. The FDA has gained some relief from such constraints by developing a measure of authority to turn the "clock" on and off.

Similarly, the authorization of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and reauthorization of the Resource Conservation and Recovery Act (RCRA) determined certain priorities for the ATSDR, which has responsibility for assessing potential risks to human health posed by landfills and surface impoundments. The ATSDR is required to give priority to requests where there is documented evidence of release of hazardous substances, the potential risk is highest, and the administrator of the ATSDR believes that existing assessments are inadequate.

The NIOSH (CDC), which was established in the department by the Occupational Safety and Health Act of 1970, is instructed to produce criteria that describe "safe" exposure levels for persons whose work requires exposure to toxic materials and harmful physical agents and substances. The 1977 Mine Safety and Health Act contains similar instructions. In both, the NIOSH must be responsive to the needs of outside agencies, particularly the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA) in the department of labor. However, the NIOSH has some freedom to set its own agenda and to negotiate about the specific hazards to be evaluated and the time frame of the reviews. Its criteria documents identify hazards and their respective magnitudes and provide a framework by which the OSHA and MSHA can order their priorities for regulatory consideration.

Most DHHS units are not subject to such statutory constraints; priorities for risk determination are more directly controlled by unit and departmental mandates (including congressional interests identified in appropriations bills), staff needs, the nature and amount of data available, tolerable levels of uncertainty, perceived urgency of controlling a hazard, and the public health responsibility concerning the anticipated magnitude of impact on the affected populations. The NTP (OASH) selects chemicals for toxicity testing on the premise that industry will test chemicals for health and environmental effects as intended and mandated by law; consequently, the NTP has generated its own set of principles, different from those implicit in industrial testing, to guide its selection of substances for evaluation. The NTP Chemical Selection Committee has adopted highly structured approaches to determining data needs and to making decisions about the objective ranking of chemicals for carcinogenicity testing. Those priority rankings are reviewed by the NTP board of scientific councilors, which adds a high-level subjective consensus judgment in the last phases of decisions about which compounds to test.

For many units of the DHHS, the stimulus to perform risk assessments come from the broader mandate of the Public Health Service (PHS) to protect and promote public health and to heal disease. Risk assessments help staff to decide research orientations, determine types and degrees of intervention, establish new diagnostic methods, promulgate novel treatment regimens, select optimal health promotion policies, and decide on the information content of tools by which to educate the public. Two factors are viewed as particularly valuable in setting priorities for undertaking risk determinations: the severity of the disease and size of the population at risk.

The known or anticipated severity of a disease or injury has a strong influence on priorities for risk assessment. Because cancer is a dreaded disease, with devastating personal and societal effects as well as generally poor outcome of treatment, there is a sense of urgency in determining the carcinogenic potential of individual chemical compounds (e.g., ethylene dibromide by CCERP) and lifestyle characteristics (e.g., dietary fat by NCI). Various units, therefore, perform or support risk assessments of hazards that are small for any one person, but may affect many people (e.g., carcinogenic risks associated with mammography as evaluated by NIH). Experts generally acknowledge that processes for assessing cancer risks are technically more advanced than processes for other diseases, perhaps because of the high priority generated by a sense of severity.

Fear of other crippling and fatal diseases, such as epidemic swine flu, is sometimes the compelling factor behind a decision to assess health risks. Such fear has been instrumental in decisions to engage in various components of risk assessment by several DHHS units, particularly the CEH (CDC), NIOSH (CDC), NCI (NIH), NIEHS (NIH), NTP, and FDA.

Also persuasive in setting priorities for risk assessments is the expected size of the impact of some hazard on the population. For example, much of the U.S. population is exposed to tobacco smoke from passive smoking. To the extent that passive, as well as active, smoking might contribute to cancer and cardiovascular disease, public health concerns are large. Hence, the OSH (OASH) continually evaluates the weight of the evidence regarding risks from passive smoking. Similarly, concern over low-level but widespread contamination by EDB of foods made from grain products influenced the decision to have the CCERP (OASH) review several governmental risk assessments of this pesticide. Likewise, special consideration was given by the NIH to the ongoing assessment of carcinogenic (NCI) and cardiovascular (NHLBI) risks from consumption of dietary fats.

Although agency oversight of most department activities that set priorities for risk assessments appears to be acceptable, the irregularity of systematic planning procedures for the efforts may lead to unnecessary delays, inefficiencies, and perhaps some strain on public credibility and confidence in the processes. The formalization and improvement of mechanisms for setting priorities and for other planning procedures within individual agencies would facilitate greater programmatic control by each agency, enhance overview of departmental activities useful to the secretary, and serve as a resource for the sharing among DHHS units of advances in approaches to the planning process.

Data Needs

DHHS units differ widely in the minimum amount of data that they require before they will or can undertake a comprehensive assessment of health risks. Some units require that human data support the associations between disease and suspect etiologic agents before they initiate a risk assessment activity such as a consensus development conference (e.g., the carcinogenic risk associated with mammography); others try to evaluate impacts on the health of the nation from the results of a few studies in laboratory animals while epidemiologic data are still sparse or nil (e.g., assessments of EDB). Human data are commonly relied on during the hazard identification step, while other data are used if the human data are judged to be of insufficient quality or quantity. The hazard characterization phase frequently relies on epidemiology and animal studies developed from the conclusions reached during hazard identification. DHHS units divide exposure characterization into two categories: characterization of the population exposed and characterization of the exposure itself.

Each unit of the DHHS uses all available health data as it develops a risk assessment. However, the quality and quantity of available data vary widely from one risk assessment to another; mainly animal data were used for the assessment of D&C Green No. 6 by the CFSAN (FDA), while both animal and human data were used for assessments of EDB by the NIOSH (CDC). Data also vary from one stage of the risk assessment to another, as when no data were available for the FDA's Center for Devices and Radiological Health (CDRH) to estimate the number of people likely to receive orthopedic implants.

The nature and amount of available data clearly determine the level of certainty one can have in the results of an evaluation. Thus, some conclusions are stated as "suspicious" only, some as "indications," others as "probable," and still others as "proven" within the constraints of scientific feasibility. Because all units look for data to provide them with the greatest feasible degree of certainty in an assessment, human data are generally accorded more importance than animal data of similar quality, and more credence is given to data from studies with better design and execution. Of course, such differences in weighting will vary among risk assessments depending upon both scientific and risk management considerations. Often human data are inadequate because of one or more design flaws. In such cases, well designed and executed animal studies assume greater importance than those in humans. Such data are carefully analyzed to determine the degree of consistency among all data elements, both to serve as a basis of delineating uncertainties in the risk determination and to guide formation of increasingly sophisticated data bases.

Staff Needs

The number of substances or hazards for which an agency might want or need a health risk assessment generally exceeds the personnel resources available for such tasks, so that inadequacy of available manpower or shortage of specific technical skills may impede the timely development of needed health risk assessments. In addition, professionals particularly suited to performing certain types of risk determinations are relatively scarce because such individuals are less the product of formal education than of insight gained through specialized experience within the units. The range of expertise in DHHS units varies considerably.

The NIH and other DHHS units commonly support outside risk assessments by means of contracts or grants, though it is not clear how much this reflects deficiencies in staff numbers and expertise. Some units supplement their own capabilities by direct assistance (usually temporary) from sister units. For example, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) collaborated extensively with the NCHS (OASH) to develop a component of NCHS's Health and Nutrition Examination Surveys and National Health Interview Surveys that deal with alcohol use. Individual programs sometimes assist each other, as in joint surveys by the NIAAA and NIDA (both programs of ADAMHA) on alcohol use among young people. However, such assistance may place substantial stress on the supporting unit and cannot be sustained without affecting the capability of the contributing group to meet its other responsibilities.

The makeup of the teams involved in DHHS risk assessment appears to vary more with the agency involved than with the problem at hand. There exists a pattern or reasonably fruitful exchange of expertise among agencies around specific technical issues, but there is a need for a longer corps of trained talent available to undertake the various tasks of risk assessment, particularly those in risk determination. Despite the skewing of expertise in particular agencies, outcomes to date have generally not been adversely affected.

Organizational Placement and Channels

The location of risk assessment staff within a larger unit, and whether or not a risk assessment group is even formally designated, varies considerably from one agency to another, depending on the mandates of a unit, the number and scope of risk assessments needed, and the relative importance placed on risk assessment by management. Some agencies have designated special groups, such as the FDA's Cancer Assessment Committee and the CCERP's Subcommittee for Ad Hoc Chemical Risk Assessments, to perform formal risk assessments with staff identified in organizational descriptions; other units do not formally recognize a specific organizational entity for such a function.

An organizational concept used by some units is the appointment of ad hoc risk assessment groups. The NIH convenes a consensus development conference only on request by a specific Institute. The FDA similarly makes irregular though substantial use of the FASEB to address risk and safety issues.

Most risk determinations are forwarded to the subunit director, who then sends assessments and policy statements to the unit director. If a topic encompasses a large segment of the population or is considered controversial, the assessment may be sent to still higher levels, and some reach the secretary of the DHHS for action decisions.

There exists within the DHHS a high degree of informal communication about health risk assessment activities, but no cohesive departmental pattern for determining risk or reporting results of determinations. An improvement in the systematic performance of a variety of specific functions is needed to enhance the use of resources available for department risk assessment efforts: (1) exchange of information about methods, approaches, and reports; (2) formal liaison with other parts of government involved in these activities; (3) maintenance of an accessible record of risk assessments completed and underway; (4) maintenance of a roster of competent risk analysts within the DHHS; and (5) circulation of information on advances in methodology or data.

While there is merit in continuing the flexibility of the current decentralized approach of DHHS agencies to determining risk, more active coordination could help agencies develop and implement their own policies, foster more uniform procedures where possible and desirable, and develop more uniform means of reporting the results to decision makers.

Scientific Review

All units of the DHHS use scientific review in the risk assessment process, though the process is more formal and extensive in some units than in others. Informal mechanisms for scientific review involve communication and consultation among scientists. Assessments used primarily for research are usually peer-reviewed by the scientific community at large, including peer review prior to publication in leading journals.

Formal review processes may be either intramural or extramural, and are specific to each unit as well as to the type of risk assessment. Intramural reviews vary in breadth from departmental to subunit only while extramural reviews tend to consist of scientific review by peers. Assessments used for public information and information transfer usually receive extramural peer review, while assessments used for regulation are always available for extramural review by the public at large following *Federal Register* notifications.

Certain groups seek no outside review of the technical merit of a risk assessment, because it is presumed that those involved are national experts in the field, as in the case of the RAC and consensus development conferences, and that additional review would not increase either the reliability or credibility of conclusions.

When technical reviews are invoked, they occur almost exclusively at the end of the risk determination process. Despite certain clear advantages, such scheduling introduces some liabilities, as when pursuing an outdated analytic technique or having missed some critical data. Earlier scientific review, even in the planning phase, might often be helpful.

SUMMARY

While many common themes emerge from the analysis of risk assessment activities within the DHHS, variety is its hallmark. Disparities can result from differences outside the control of the generating unit, including differences in the nature and mandate of the unit and differences in the purpose or use of the risk assessment. The four-component framework for the risk assessment process applies throughout, however, and it has provided a means for comparing units of the DHHS, though units differ in which components are used and to what degree.

Among the issues showing substantial variation from issue to issue and unit to unit are (1) specific methods used for setting priorities (all units set priorities, but the driving forces range from specific statute, to general mandate, to desire to protect public health and heal disease); (2) data needs required for the risk assessment (all units use all available data, but large variations in data quality and quantity determine differences in the level of certainty in the assessment); (3) staff needs (staff used for risk assessments range from internal to external to a combination); (4) organizational placement (placement of assessors within the generating unit depends on mandate, number and scope of assessments, and importance placed on risk assessment); and (5) scientific review (all units do reviews, but they range from short, though thorough, internal reviews to extensive external reviews).

The risk determination component shows the most heterogeneity, often for reasons outside the control of the generating units.

Determinations are expressed in a variety of ways, from general qualitative statements to complex quantitative estimates including risk-benefit analyses. Because many risk determinations are arrived at by agencies—particularly those related to voluntary risks that are to be addressed through public education efforts—they are not acknowledged as risk assessment efforts and are often approached almost informally. Such determinations might be improved by a more structured process.

On rare occasions the full range of scientifically reliable and applicable data available is not incorporated into the assessment process. More uniform procedures would be advantageous for the interpretation of hazard and exposure information of varying quality and strength to assure the consistency, technical soundness, and credibility of the risk assessments.

Though a clean separation of risk determinations from risk management issues may be desirable in theory, it is often difficult in practice. All risk determinations require the application of various assumptions to reach conclusions, and while many of these assumptions have a biologic foundation, the management implications of issues sometimes influence the selection of analytic choices. Risk management consideration may also legitmately affect risk determinations in setting priorities and in determining the format of reporting.

Scientific uncertainties arise throughout the analysis of health risks and influence the nature and strength of the risk conclusions, yet there is no uniform way of dealing with uncertainty in reporting the outcome of various health risk assessments; often the question is not addressed at all. Because many risk assessments involve situations in which sharp differences of scientific interpretation are unavoidable, opinions may vary on the appropriate conclusions. Occasionally the full range of opinions may not be adequately reflected in recommendations forwarded for decision.

Chapter 10

RECOMMENDATIONS

Risk assessment—the qualitative or quantitative estimation of the likelihood of adverse effects from exposure to specified health hazards or from the absence of beneficial influences—is widely practiced throughout the Department of Health and Human Services (DHHS). The scope and importance of DHHS activities to determine health risks has grown beyond the point where risk assessment can be treated as a narrow discipline. It is now a major departmental activity, and the recent trend of growth is likely to continue. This volume, with the report of the Executive Committee of the Committee to Coordinate Environmental and Related Programs (CCERP) on risk management of toxic substances, provides the first department-wide review and basis for further evaluating DHHS policies regarding risk assessment as a whole.

An evaluation of the descriptions and examples of health risk assessment activities throughout the DHHS shows that, in general, the agencies make health risk determinations in a responsible manner but that opportunities remain for improvement, particularly at levels that cross Public Health Service (PHS) agencies. Differences exist in the procedures used to make determinations about health risks that cannot all be explained by variations in the nature of the problems addressed or the types of information available for analysis. Measures can be implemented to improve communication among agencies and to enhance the insight of decision makers into critical elements of the analyses—for example, the strength of the data base involved, the level of uncertainty affixed to the conclusions, or the management implications and options that must draw on more than just risk assessments for a given problem. Of special importance is the need for improved understanding on the part of the general public about the nature and the meaning of various risk determinations. Public confusion about these matters can translate into public fear or public apathy, either of which can interfere with rational and responsible risk management policy.

The evaluation also shows that often there are unavoidable gaps in information needed for a complete and comprehensive assessment. Consequently, the more limited the data, the more uncertain the risk management decision. Nevertheless, risk management decisions must be made, however constrained by the precision or accuracy of the tests and methods used. The recommendations below do not address the problem of data gaps, but do suggests ways to improve the risk assessment process, which, in turn, should aid the risk management decision process. Recommendations are presented in the following four major areas and contain principles that should be considered for their implementation: (1) agency conduct of risk assessment processes; (2) coordination and collaboration of DHHS risk assessments; (3) presentation of risk determinations above the agency level; and (4) public understanding or risk assessments.

One must continually bear in mind the sharp distinction between risk assessment per se and research, which supplies many of the critical inputs for risk assessment. The following recommendations apply only to the formal process reaching a conclusion about risk, not to the conduct of research.

AGENCY CONDUCT OF RISK ASSESSMENT PROCESSES

Individual PHS agencies are responsible for managing the often complex processes that lead to a risk determination. Comprehensive risk assessments used to determine the need for and direction of administrative or regulatory actions generally undergo several stages of development, both informal and formal. Informal efforts often include preliminary evaluations that establish whether a formal assessment is warranted. By contrast, formal efforts may require highly structured and thorough analysis of all potentially relevant hazard and exposure information. Proper planning enhances the likelihood of completing a risk assessment that is comprehensive, objective, and timely.

Such planning need not be lengthy or expensive but includes key *a priori* considerations such as the (1) needs for the assessment and acknowledgment of implications of the problem; (2) discussion of the intended and expected uses of the assessment; (3) delineation of the scope of the intended risk assessment; (4) identification of information needs and resources; (5) elucidation of technical issues lifely to pose serious or unusual difficulties, and identification of optional approaches to those issues; (6) exposition of relevant policy issues, including relevance of existing unit policies, identification of any useful precedents, and optional approaches to unique policy issues; (7) composition of expertise of the risk assessment team, determination of team needs, nomination and selection of team members, designation of leader and spokesperson, and determination of level of involvement of team members; (8) determination of a schedule for completion and anticipated impacts of schedule alterations; (9) description of internal and external review mechanisms and rationale for each; and (10) plan for distribution of results.

Recommendation 1. Each PHS agency should develop and implement guidelines for the conduct of the health risk assessments it undertakes as a basis for regulatory, service, or educational risk management strategies. The following principles should be considered in the development of such guidelines:

- As each PHS agency identifies a candidate for a formal risk determination, it should develop a plan that addresses the full range of activities required for an appropriate assessment effort.
- Agency determinations of risk on a given subject should be performed by experienced professionals with adequate collective background knowledge in each of the major components of risk assessment, and led by an individual skilled at integrating that knowledge.
- Risk assessments should incorporate all scientifically reliable and relevant data, or be explicit about why data were or were not used.
- A hierarchy of information—human data predominating except when lacking characteristics important to risk determination—should continue to be used in performing risk assessments, and agencies should remain both flexible and objective in selecting findings pivotal to the risk conclusions.
- Risk management issues should rarely affect the analytic choices in risk assessment. Where influence of risk management is unavoidable, this should be explained in the report of the risk determination.
- Every formal risk determination should involve a formal effort to characterize the strength of the evidence, as well as the sources, nature, and impact of attendant uncertainties in the analysis.
- Policies and procedures should be established at the agency level to ensure that reports on each risk assessment accurately

reflect the consensus, as well as the minority opinion should one exist.

- Full and complete disclosure of the risk assessment processes and the information relied upon should be practiced by each agency.
- Internal and external review, including public consultation, should be applied to the risk determinations where appropriate.
- Technical reviews—at least internal—should be incorporated in risk determinations from the outset.

COORDINATION AND COLLABORATION OF DHHS RISK ASSESSMENTS

Communication and coordination within the department is central to continued refinement and improvement of risk assessment. Particularly vital functions include coordination among units on scientific developments that influence the analytics of risk determination, sharing scientific expertise, coordination with agencies outside the DHHS on the applications of risk determinations, setting priorities for risk determinations within the department, determining departmental procedures for review of risk determinations, and utilizing the skills of DHHS professionals in risk assessment.

More active coordination of DHHS health risk assessment activities may (1) help to provide the secretary and other key decision makers with an early warning about certain critical risks that may be brought to their attention; (2) assure appropriate cross-agency collaboration for risk assessments of public health issues common to more than one agency; and (3) provide an opportunity for improving the form, method, and usefulness of risk assessment presentation to the assistant secretary for health and the secretary. These goals could be approached in a variety of ways, ranging from the creation of a separate office to expanding the mandate of an existing committee such as the executive committee of the CCERP. Most task force members favor the latter.

Recommendation 2. A coordinative mechanism should be designated in the PHS to enhance internal and external coordination, internal collaboration, priority setting, and review procedures related to departmental efforts in risk assessment. The following principles should be considered in the operation of any such coordinative mechanism:

- Emphasis should be placed on those issues that cut across agency jurisdictions and activities.
- The current flexibility of PHS agency efforts to determine health risks should be preserved, given the differences in mandates, issues, and approaches that characterize their activities.
- The coordinative mechanism should be facilitative, not directive, in helping individual agencies develop their own guidelines for the conduct of risk assessments.
- A major priority of the coordinative mechanism should be the development of a format for presenting the results of risk determinations, and the limitations that exist, to policymakers such as the Secretary and the Assistant Secretary for Health.

PRESENTATION OF RISK DETERMINATIONS ABOVE THE AGENCY LEVEL

Any risk assessment, no matter how technically sound and scientifically supportable, may fail to contribute to the general DHHS mission of protecting public health unless risk managers can understand and interpret it in the context of considerations beyond the health impact itself. Therefore, the method of presenting the results of a risk determination takes on special importance.

Confidence in risk conclusions depends on the strength of the evidence regarding cause-effect relationships, the internal consistency of the data base, the state-of-the-art characteristics of individual studies, and the concordance of findings of hazard with plausible biological explanations for those findings and for their application to other situations. Confidence may be influenced by the choice of a safety factor whose magnitude is selected knowledgably but subjectively.

The manner and extent to which the decision maker is informed about the analytic content of these various dimensions can have a considerable bearing on the clarity, reliability, and degree of confidence with which a decision can be made. Also important for the risk manager is the analysis of such considerations as whether or not to manage and by what means. Guidelines for the format and content of a risk determination to be used in a risk management decision by a policymaker who may not be intimately familiar with the analytic procedures could facilitate responsible decision making, by creating standard approaches for orderly and useful review of the risk determination.

Recommendation 3. General guidelines for format and content should be developed for use in reporting the results of risk determinations for risk management decisions above the agency level. The following principles should be considered in the development of such guidelines:

- The presentation should include a clear statement of the nature of the hazard and the determination of the extent of risk.
- To the extent possible, the presentation should place the magnitude of the risk within an understandable context (e.g., on an intensity spectrum, or in a comparative mode).
- The process of arriving at the determination should be summarized, including the types of expertise involved, the review processes employed, and any divergencies in relevant points of view or conclusions.
- A summary comment should be offered on the nature and quality of the data and, if relevant, the power and limitations of the analytic models applied.
- The presentation should include a specific statement about the magnitude, sources, nature, and possible impact of uncertainties in the determination.
- The format should provide for a presentation of options as well, and should take into account the different regulatory and legislative mandates of the specific agency, as well as the projected impacts.

PUBLIC UNDERSTANDING OF RISK ASSESSMENTS

Effective management of health risks often requires a good public understanding of the nature and degree of risk, as well as of the processes of assessing and making determinations about those risks. Certainly this is true for intervention strategies that are strictly educational in nature and designed to motivate behavior change, but it is also true for regulatory interventions. Public confidence in the regulatory process is shaped substantially by the public's perception of the credibility of the agency, and therefore, by the perception of the agency's procedures as rational, responsible, and open.

Unfortunately, public understanding of the nature, potential, and limitations of the risk assessment process is often weak. Without such understanding, an erosion of support for risk management decisions and diminution of public confidence in the scientific establishment can occur.

Recommendation 4. Efforts should be made by each PHS agency to provide information to the public on the assessment of specific hazards, the nature of health risks in general, and DHHS risk assessment procedures. The following principles should be considered in the development of efforts to improve understanding of health risks:

- Where appropriate, the public should be informed about, and/or involved in, the planning and conduct of health risk assessments.
- For any given determination of a specific health risk, efforts should be made to place the risk in an understandable, comparative context.
- In providing information on comparative risks, efforts should be made to compare involuntary risks to other risks of an involuntary nature.
- Agency efforts to improve public understanding of health risks should be multifaceted, using informational materials, work with science writers, public briefings, and other activities that may be appropriate for specific purposes.

Appendix 1

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ACS	American Cancer Society
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
ADI	acceptable daily intake
AIDS	acquired immune deficiency syndrome
AN	analgesic nephropathy
AOA	Administration on Aging
ARC	Addiction Research Center
ARUS	Alcohol Research Utilization Systems
ASH	Assistant Secretary for Health
ATSDR	Agency for Toxic Substances and Disease Registry
BCDDP	Breast Cancer Detection Demonstration Project
BEIR	Biological Effects of Ionizing Radiation
BERC	Bureau of Eligibility, Reimbursement, and Coverage
BID	Bureau, Institute, or Division
BNA	Bureau of National Affairs
CAC	Cancer Assessment Committee
CCATT	Coordinating Committee on Assessment and Transfer of Technology
CCERP	Committee to Coordinate Environmental and Related Programs
CDB	Center for Drugs and Biologics
CDC	Centers for Disease Control
CDRH	Center for Devices and Radiological Health
CEC	Chemical Evaluation Committee
CEH	Center for Environmental Health
CEQ	Council on Environmental Quality
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations

CFSAN	Center for Food Safety and Applied Nutrition
CHD	coronary heart disease
CHPE	Center for Health Promotion and Education
CID	Center for Infectious Diseases
CIS	Central Information System
CNS	central nervous system
CPPT	Coronary Primary Prevention Trial
CPS	Center for Prevention Services
CPSC	Consumer Product Safety Commission
CVM	Center for Veterinary Medicine
DDE	dichlorodiphenyldichloroethylene
DDR	Division of Research Resources
DDT	dichlorodiphenyltrichloroethane
DES	diethylstilbestrol
DHHS	Department of Health and Human Services
DOD	Department of Defense
DOL	Department of Labor
DPCP	dibromochloropropane
DRG	Division of Research Grants
DSDTT	Division of Standards Development and Technology Transfer
DSHEFS	Division of Surveillance, Hazard Evaluations, and Field Studies
DSR	Division of Safety Research
DT	diptheria, tetanus
DTP	diptheria, tetanus and whooping cough/pertussis
ECA	Epidemiologic Catchment Area
ECG	electrocardiogram
EDB	ethylene dibromide
EMTD	estimated maximum tolerated dose
EPA	Environmental Protection Agency
FAS	fetal alcohol syndrome
FASEB	Food Additive Safety Evaluation Branch
FDA	Food and Drug Administration
FOI	Freedom of Information
FSH	follicular stimulating hormone
GI	gastrointestinal
GPO	Government Printing Office
GRAS	generally recognized as safe
HCFA	Health Care Financing Administration
HDL	high density lipoproteins
HDL-C	high density lipoprotein-cholesterol
HETA	Hazard Evaluations and Technical Assistance
HHE	Health Hazard Evaluation

HIP	Health Insurance Plan
HMO	Health Maintenance Organization
IBC	Institutional Biosafety Committee
IDE	investigational device exemption
IND	Investigative New Drug Application
IOM	Institute of Medicine
IRB	Internal Review Board
IRLG	Interagency Regulatory Liaison Group
IRMG	Interagency Risk Management Group
IUD	intrauterine device
JAMA	*Journal of the American Medical Association*
LDL	low density lipoproteins
LDL-C	low density lipoprotein-cholesterol
LET	linear energy transfer
LH	luteinizing hormone
LRC	Lipid Research Centers
6MC	6-methylcoumarin
MMWR	*Morbidity and Mortality Weekly Report*
MOS	margin of safety
MRFIT	Multiple Risk Factor Intervention Trial
MSHA	Mine Safety and Health Act
MTD	maximum tolerable dose
NADA	New Animal Drug Application
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NCHS	National Center for Health Statistics
NCHSR/HCTA	National Center for Health Services Research and Health Care Technology Assessment
NCI	National Cancer Institute
NCTR	National Center for Toxicological Research
NDA	New Drug Application
NEI	National Eye Institute
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIADDK	National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDR	National Institute on Dental Research

NINCDS	National Institute of Neurological and Communication Disorders and Stroke
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NMR	nuclear magnetic resonance
NOEL	no-observed-effect level
NRC	National Research Council
NSF	National Science Foundation
NTIS	National Technical Information Service
NTP	National Toxicology Program
OASH	Office of the Assistant Secretary for Health
OBRR	Office of Biologics Research and Review
ODRR	Office of Drug Research and Review
ODS	Office of Drug Standards
OHTA	Office of Health Technology Assessment
OMAR	Office of Medical Applications of Research
OPRR	Office of Protection from Research Risks
ORDA	Office of Recombinant DNA Activities
OSH	Office on Smoking and Health
OSHA	Occupational Safety and Health Administration
OSTP	Office of Science and Technology Policy
OTA	Office of Technology Assessment
OTC	over the counter
P/S Ratio	polyunsaturated fat to saturated fat ratio
PBB	polybrominated biphenyls
PC	probability of causation
PCB	polychlorinated biphenyls
PCP	phenyclidine
PHS	Public Health Service
PMA	Pharmaceuticals Manufacturers Association
PTCA	percutaneous transluminal coronary angioplasty
Q-Factor	quality factor
RAC	Recombinant DNA Advisory Committee
RCRA	Resource Conservation and Recovery Act
RAUS	Research Analysis Utilization System
RBA	risk-benefit analysis
RFA	request for application
SAR	structure-activity relationship
SEER	Surveillance, Epidemiology, and End Results
SI	special intervention

SIDS	sudden infant death syndrome
SOM	sensitivity of method
TCC	Technology Coordinating Committee
TCDD	2,3,7,8-tetrachlorodibenzodioxin
THC	delta-9-tetrahydrocannabinol
TIC	Technical Information Center
TSS	toxic shock syndrome
TWA	time-weighted average
Total-C	total cholesterol
UC	usual care
UK	United Kingdom
USDA	United States Department of Agriculture
USUHS	Uniformed Services University of the Health Services
VA	Veterans' Administration
VSD	virtually safe dose
VTD	video terminal display
YAG	neodymium–yitrium–aluminum garnet laser

Appendix 2

GLOSSARY

NOTE: *These definitions are limited to context(s) in which the terms are used in this publication. Some terms (e.g., "assay") have substantially broader or different meanings in other contexts.*

absolute risk model A model that predicts the additional number or proportion of persons affected, or a difference from background, by a given level of exposure to a hazardous agent. (See also relative risk model.)

acceptable dose See safe dose.

acute Referring to a brief, often high level of exposure or dose; a health effect that results from brief exposure; or an experimental study designed to investigate the short-term health effects of a hazard.

additive A risk model in which response following exposure to particular levels of two or more hazards is equal to the sum of the responses to each hazard alone.

ADI Abbreviation for Acceptable Daily Intake. An amount of a hazardous substance that is thought to be "safe" (q.v.) in that daily exposure will not cause adverse health effects.

ambient dose The exposure of a person to a hazard from the surrounding environment.

Ames test An in vitro test of the capacity of a substance to produce mutations in the bacterium Salmonella typhimurium, generally used as a rough measure of carcinogenicity.

assay The qualitative or quantitative evaluation of the hazardousness of a substance; the results of such an analysis. (See also bioassay.)

atmospheric dispersion The spreading of a substance through the atmosphere from a source via air currents and diffusion.

background rate The level, often low, at which some substance, agent, or event is present or occurs at a particular location and time in the absence of a hazard under study.

Bayesian inference A specific approach to statistical inference that accommodates prior knowledge, including subjective probabilities. A formal Bayesian analysis leads to probabilistic assessments of uncertainty.

behavioral risk factor A characteristic or behavior of a person that is predictive of an increase or decrease in the risk of a particular adverse health effect; the term does not imply cause and effect.

benefit-risk See risk benefit analysis; risk benefit ratio.

best estimate An estimate of health outcomes that is judged to reflect (in some way that must be specified in each application) the most likely levels of exposure and response to a hazard.

"best friend" control In case-control studies (q.v.), a person designated by a subject as the subject's "best friend" (and hence more likely than average to be subject to similar background influences).

bias The difference, generally unknown, between the expected (average) value of some estimate of a parameter and its true value.

binary A variable having only two possible values, such as on or off, or 1 or 0.

bioassay The quantitative evaluation of the effects of a substance by assessing its effects on live experimental animals or on humans.

biocompatibility A condition in which a substance (e.g., a hip implant) does not have a toxic or injurious effect on a biological system.

biomarkers Biological markers; biologic indicators (such as DNA damage) of either past exposure to a hazard or the future likelihood of toxicity or other adverse effects.

biopsy Removal and examination, usually microscopic, of tissue from the living body.

case-control study A study in which groups of individuals are selected because they do (cases) or do not (controls) have a condition under study. Comparisons between groups are generally made in terms of characteristics that might have caused the condition. See also cohort study.

chronic An effect or symptom that persists for a long time or takes a long time to manifest itself; a study designed to examine such effects or symptoms; prolonged exposure (often at low levels) to a hazard.

clinical pharmacology Investigation of the physical and chemical properties, mechanisms of action, absorption, distribution, biotransformation, and excretion, and therapeutic and other uses of drugs by observing their effects directly in humans.

clinical trial A controlled experiment on human subjects to determine or compare the effects of different medical treatments, sometimes including placebos or no treatment.

cocarcinogen An agent that increases the overall carcinogenic risk when administered together with a specific carcinogen.

cohort study A study of research subjects classified on the basis of characteristics present prior to the appearance of the condition under study. The cohort groups are observed over a period of time to determine the frequency and/or severity of the condition under study. See also case-control study.

communicative disease A disorder in normal processes of human communication, often as a result of a neurological or psychiatric disease.

concentration gradient The distribution, across either time or space, of the concentration of a specified substance (e.g., in ambient air).

concern level A classification system used by the Center for Food Safety and Applied Nutrition to determine toxicological testing requirements for food additives according to their overall potential for adverse health effects.

confounding variables Variables not of direct interest in a specified study but whose variation may induce, conceal, or distort an association between variables of interest and the disease condition. The effects of confounding variables can often be reduced or controlled by appropriate selection of subjects and statistical treatment of the data.

control Group of experimental animals or humans who were not exposed to an agent under study. The frequency of the disease in these individuals is used to estimate the background rate (q.v.) in the corresponding study group.

correlation A measure of the degree to which variables change together, usually taken to mean a linear relationship; a measure of the intensity of association.

Criteria Document A document developed to provide the technical bases ("criteria") needed for a regulatory agency to set exposure levels for a hazardous substance.

cross-sectional study A study in which measurements of possible causes and effects are made at the same time; see also longitudinal study.

decision analysis A formal process of identifying, analyzing, and comparing the effects of each of a specified collection of possible actions.

Delaney Clause An amendment of the Food, Drug, and Cosmetic Act (Sec. 409(c)(3)(A) that effectively prohibits the use as a food additive of any substance found to be carcinogenic.

detoxify To reduce or eliminate the toxic properties of a substance, usually by metabolic processes that produce a compound that is less toxic or more readily eliminated.

dizygotic twins Twins derived from two separate and separately fertilized ova: fraternal or non-identical twins.

dominant-lethal mutation A gene mutation that results in death of the organism regardless of whether or not the gene is paired with another similarly mutated gene.

dose response modeling The process of characterizing the relationship between the dose of drug or hazard and the health effects caused by that dose.

dose response relationship The relation, often expressed as a graph or a mathematical function, that characterizes the frequency or intensity of a health effect across a range of doses.

dosimetry The measurement or estimation of doses.

dosage (dosing) regimen The amount of a foreign entity, the route, and the time course over which it is administered to an organism.

ecologic analyses Analyses based on data derived from aggregated or grouped data. Often, errors in inference arise because the appearance of important effects is created or masked by the aggregation process.

embryotoxic Increasing the risk of an adverse health effect in a developing embryo when administered to a gestating animal.

endogenous factor A factor arising in an organism that causes or contributes to a particular health effect. An example is genetic susceptibility to a disease. See also exogenous factor.

epidemic A disease or condition that is either spreading rapidly and extensively among many individuals in a population or is already widespread among individuals in that population.

epidemiologic study A study of the distribution and determinants of disease in humans based on the observation of populations in a non-experimental situation.

etiology The science of the origin, causes, and development of diseases.

exogenous factor A factor originating from outside an organism (e.g. from ambient air) that causes or contributes to a particular health effect.

explant Tissue taken from the body of an organism and grown outside the body in an artificial medium.

exposure The amount of a foreign entity that an organism comes into contact with; distinct from dose, which is the amount that enters or interacts with the organism.

exposure assessment The qualitative or quantitative determination of the amount of a foreign entity a person or population comes into contact with.

exposure characterization The qualitative and quantitative evaluation of the degree of human exposures to a hazardous agent.

extramural research Work supported by a government agency but undertaken elsewhere; generally with financial support by means of a government grant or contract. See also intramural research.

extrapolation Prediction of the value of a variate outside the range of observation.

family studies Epidemiological studies using and comparing members of the same family as subjects.

gavage Forced feeding of a test animal, usually through a tube passed into the stomach.

hazard A substance or condition that may adversely affect human health.

hazard characterization The qualitative and quantitative evaluation of the nature of the adverse effects of a hazard, including their expression as functions of the amount of exposure (dose) (q.v.)

hazard identification The qualitative indication that a substance or condition may adversely affect human health.

hazardous waste Corrosive, ignitable, explosive, or toxic waste that poses a hazard to humans or the environment.

health care technology A discrete, identifiable regimen or modality used to diagnose or treat illness, prevent disease, maintain well-being, or facilitate or improve the application of health care services.

heterozygous The state of having two different genes at a given locus.

high to low dose extrapolation Prediction of the frequency of an adverse health effect caused by low doses of a hazard by using the results of experiments conducted at much higher doses.

homozygous The state of having two identical genes at a given locus.

in vitro In an artificial environment outside the living organism, usually referring to experiments.

in vivo In the natural environment or within the living organism, usually referring to experiments.

incidence The extent or frequency of a particular event or condition; usually applied to an adverse human health effect.

in-house manual or periodical A publication (e.g., *The Schizophrenia Bulletin, The Psychopharmacology Bulletin*) produced by the staff of an agency to report results of some intramural or extramural activities.

initiator A substance that causes the first step(s) in a multi-step process of carcinogenesis.

insignificant level of risk That level of risk incurred by an individual which is deemed not to cause a consequential change in the likelihood of adverse effects. Typically, the value specified for this level is 1 in 100,000 to 1 in 10,000,000.

integrated exposure assessment The quantitative estimation of human exposure to a hazard from all possible sources and by all possible routes, and/or human exposure to all possible hazards.

inter-risk comparison Comparison of estimated or actual risks from different hazards; often used to help rank the severity of hazards and to set regulatory and policy agendas.

interpolation The prediction of the value of a variate within the range of observation.

interspecies conversion The conversion of doses used in animal bioassays to doses that may be equivalent (in some sense usually not specified) in humans.

intramural research Research performed by staff members of a government agency. See also extramural research.

invasive potential The ability of a microbe or other organism to enter the body and spread, usually causing adverse health effects. Also the ability of cancer cells to spread by direct growth into adjacent tissues.

latency The quality of being dormant or concealed; not being manifest yet. (See latent period.)

latent period The time between exposure to an infectious agent or other hazard and the manifestation of any adverse health effects that it causes.

lifetime risk The risk to an individual that a given health effect will occur at any time after exposure, without regard to the time at which that effect occurs.

likelihood ratio test A statistical test based on the ratio of the likelihood of occurrence of some event under two statistical models; these usually differ in whether a specific parameter or set of parameters is included.

locus The position that a gene occupies on a chromosome.

logit Also known as log-odds; the logarithm of the ratio of frequency of two different categorical outcomes, such as healthy versus sick.

longitudinal data Data collected for a longitudinal study.

longitudinal study A study in which the status of subjects is determined at two or more times for the purpose of studying changes, often to determine their causes.

macrobiotic A diet that excludes all meat and dairy products; brown rice is a staple generally supplemented by fruits and vegetables.

margin of safety (MOS) An estimate of the ratio of the no-observed-effect level (NOEL) (q.v.) to actual exposure.

maximum tolerated dose (MTD) The maximum dose that a test animal can tolerate for the duration of a bioassay without serious effects on health or survival.

microbes Animals and plants of microscopic size, including bacteria or protozoans; especially those that cause disease.

microcosm An experimental, small scale system, more or less analogous to a much larger system in constitution, configuration, or development.

millirad A unit of measurement of absorbed dose of ionizing radiation, corresponding to an energy transfer of 0.1 erg per gram of absorbing material. (rad is an abbreviation for radiation absorbed dose.)

moieties The parts or components of a mixture or compound.

multistage model A mathematical dose response model for carcinogenesis based on the theory that a specific carcinogen may affect more than one stage in the development of a cancer.

mutagenic effects assay An in vitro test of the number of mutations per unit dose of a substance in a population of bacterial cells. (See Ames Test.)

niche All the components of the environment with which an organism or population interacts.

NOEL Abbreviation for no-observed-effect level. The highest dose at which no adverse health effects are detected in an animal population.

NOEL-SF A method for setting limits to allowable human exposure by combining the NOEL (no-observed-effect Level) (q.v.), generally measured in an animal population, with a safety factor (SF) (q.v.).

one-hit A dose response model of carcinogenesis based upon the biological theory that a single "hit" at a cellular target (DNA) by some hazard initiates the series of events that eventually leads to a tumor.

orthotopic Occurring at the normal place.

pandemic A disease or condition occurring frequently over a wide geographical area, a widespread epidemic (q.v.).

passive smoking The intake by nonsmokers of tobacco smoke left in the air by smokers; includes both smoke exhaled by smokers and smoke released directly from tobacco into ambient air.

peer review Review of manuscripts for technical and scientific merit by qualified scientists prior to publication in a professional journal.

personal monitoring device An instrument attached to a person to measure the exposure of that person to a hazard(s).

phage Also referred to as a bacteriophage. A virus that infects a bacterial cell; used in genetic engineering for transferring genes from one strain of bacteria to another.

phagocytosis A mechanism by which certain animal cells, such as macrophages or leukocytes, engulf and carry particles into their cytoplasm; this often allows the cells to make the particle harmless by detoxification or other mechanisms.

phylogeny The evolutionary history or genealogy of a group of organisms.

physiologic Pertaining to the basic activities that occur in cells, tissues, and organs of living organisms.

potency The strength of a particular drug or hazard; the ratio of the dose required to elicit a specific response to the dose of some standard that elicits the same response.

prevalence The proportion of a population that is affected with a particular disease or condition at a given time.

probability of causation The probability that an observed outcome was caused by a specific known antecedent; an example is the probability that lung cancer in a smoker was caused by the smoking (and not by other possible causes).

promoter A substance that causes the last step(s) in a multi-step process of carcinogenesis.

protocol A detailed plan for a scientific experiment or study.

qualitative Referring to a subjective investigation that identifies the important factors, and often their relative importance, affecting a problem or situation under investigation.

quantitative Referring to an analysis that not only identifies the important factors but also determines the amount that each important factor contributes to the effect being studied.

randomized double blind A study design in which subjects are randomly allocated into different groups but neither the subjects nor the investigators monitoring the subjects know which subjects are in which groups.

randomized primary prevention trial A prospective study design in which subjects are randomly allocated to one of two or more groups; all members assigned to each group are treated in the same way to determine the effect of the intervention(s) on the likelihood of a specified outcome.

reactive structures Chemical structures that are similar to those of other compounds known to produce toxic effects.

regression analysis A set of statistical methods for studying a set of observations to derive relationships among variables.

regulatory Referring to analyses, risk assessments, or other activities that are used by governmental agencies to formulate and enact regulations.

relative risk model A model that predicts the increased probability of an effect, as a ratio to background, of exposure to a given level of a toxic agent. (See also absolute risk model.)

retrospective study A study comparing certain features in the history of subjects having some condition under study with the histories of subjects not having that condition.

risk The likelihood of occurrence of an event that will result in an adverse effect.

risk assessment The qualitative or quantitative estimation of the likelihood of adverse effects that may result from exposure to specified health hazards or as a result of the absence of beneficial influences.

risk benefit analysis The process of analyzing and comparing on a single scale the expected positive (benefits) and negative (risks, costs) results of an action or inaction. (See also risk benefit ratio.)

risk benefit ratio The results of a risk benefit analysis (q.v.) expressed as the ratio of risks to benefits.

risk determination The integration of the first three steps of risk assessment (hazard identification, hazard characterization, and exposure characterization) into a scientific determination of the level of risk as a basis for policy consideration.

risk factor A substance a person is exposed to or actions a person undertakes that increase that person's risk of a particular adverse health effect.

risk management The step(s) taken to alter levels of risk a person or population is subject to.

safe Having risks that are considered "acceptable" in a specified context.

safe dose A level of human exposure to a hazard that is determined to have no unacceptable harmful effects, that is, to be "safe" (q.v.).

safety factor A multiplicative factor incorporated in risk assessments to allow for unpredictable types of variation, such as variability from test animals to humans, random variation within an experiment, and person-to-person variability. Safety factors are often in the range 10 to 1000.

SCE Abbreviation for Sister Chromatid Exchange; exchange at one locus between the sister chromatids of a cell which does not result in an alteration of overall chromosome morphology; an assay used to assess the deleterious action of chemicals on chromosomes.

sensitivity of the method (SOM) The ability of a method to correctly classify a manifest characteristic; the ability to detect an outcome when that outcome has occurred; a regulatory process whereby the method used to detect a residue is selected so as to assure that risks remain within acceptable bounds or are determined with the aid of a risk assessment; the method so chosen often falls short of the maximally (technologically) feasible sensitivity.

sensitivity testing A study of how the final outcome of an analysis changes as a function of varying the input parameters in a prescribed manner.

simulation The use of a model system (e.g., a microcosm (q.v.) or a set of mathematical equations) to approximate the action of a real system, often used to study the properties of the real system.

sociodemographic variable Variables relating to the demographic (e.g., age, sex) and social (e.g., race) characteristics of an individual subject.

special risk group A subpopulation of persons who are, on the average, more sensitive to some harmful agent than the total population.

species-specific factor A factor that affects only one (or a few) specie(s) while not affecting other species.

specificity The coupling between a particular exposure and a particular health outcome.

strain A group of organisms of common ancestry.

stress A physical or emotional factor that causes bodily or mental tension and may be a factor in disease causation.

structure activity analysis The inference from the structure of a chemical that it is likely to have some biologic property.

structure-activity relationship The association of a particular biologic effect of a chemical and the molecular structure of that moiety.

subchronic Exposure of longer duration than acute, but shorter than chronic.

Superfund The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), 26 USC 4611-82, 42 USC sec. 6911a, 9601-657; federal legislation designed to pay for cleanup, containment, and damages to natural resources caused by the release of hazardous substances into the environment.

susceptibility The quality or state of being sensitive to some specified agent.

syndrome A group of signs and symptoms that occur together and characterize a particular abnormality.

synergistic Referring to a response following exposure to two or more hazards which is greater than the sum of the responses following exposure to the same levels of each hazard individually.

synergy The synergistic (q.v.) action of two or more substances.

systemic disorder A condition of an entire system of the body, such as the circulatory system.

target organs Those organs affected by a specified dose or range of doses of a particular chemical.

threshold The minimum dose of an exposure to a harmful agent that can produce a detectable physiological or psychological effect.

threshold determination The specification of the threshold.

tolerance distribution A model that assumes that each individual in a study population has some threshold level such that higher doses cause some adverse outcome and lower doses do not, and that while these thresholds may not be known for specific individuals, they can be described for the population in terms of a probability distribution.

toxic Causing adverse or deleterious effects.

toxic agent A chemical or other agent that causes or can cause adverse or deleterious effects.

toxic endpoint The adverse or deleterious health effects caused by a toxic agent.

toxicokinetics The mechanism by which chemical or physical change causes toxic effects.

transport modeling The mathematical description (modeling) of the movement of substances through various media.

twin studies Epidemiological studies that use twins (fraternal or identical) as subjects.

uncertainty factor See safety factor.

vector borne Carried by and transmitted by an organism, as a pathogen transmitted by an insect.

ventilation The process of flushing with fresh air; breathing.

vertical convection The upwards or downwards movement of air.

virtually safe dose A technical term, in certain regulatory contexts, for a safe dose (q.v.).

virulence The relative capacity for a pathogen to overcome bodily defenses.

zero risk A condition of no increase in the probability of adverse outcome.

Appendix 3

REFERENCES AND RESOURCE DOCUMENTS

Chapter 1

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1984a. Proposed guidelines for carcinogen risk assessment; request for comments. Federal Register 49(227):46293-46301.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1984b. Proposed guidelines for exposure assessment; request for comments. Federal Register 49(227):46303-46311.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1984c. Proposed guidelines for mutagenicity risk assessment; request for comments. Federal Register 49(227):46313-46321.

ENVIRONMENTAL PROTECTION AGENCY (EPA). 1984d. Proposed guidelines for the health assessment of suspect developmental toxicants and request for comments. Federal Register 49(227):46323-46331.

INTERAGENCY REGULATORY LIAISON GROUP, WORK GROUP ON RISK ASSESSMENT (IRLG). 1979. Scientific bases for identification of potential carcinogens and estimation of risks. Federal Register 44:39858. Reprinted in J. Natl. Cancer Inst. 63:141-168.

NATIONAL RESEARCH COUNCIL (NRC). 1982. Identifying and estimating the genetic impact of chemical environmental mutagens. National Academy Press, Washington, D.C.

NATIONAL RESEARCH COUNCIL (NRC). 1983. Risk assessment in the federal government: Managing the process. National Academy Press, Washington, D.C.

OFFICE OF SCIENCE AND TECHNOLOGY POLICY (OSTP). 1984. Chemical carcinogens; Notice of review of the science and its associated principles. Federal Register 49:21594.

OFFICE OF TECHNOLOGY ASSESSMENT (OTA). 1981. Assessment of technologies for determining cancer risks from the environment. U.S. Government Printing Office, Washington, D.C.

Chapter 2

AMES, B. N. 1979. Identifying environmental chemicals causing mutations and cancer. Science 204:587.

CRUMP, K. S., et al. 1976. Fundamental carcinogenic processes and their implication for low-dose risk assessment. Cancer Res. 36:2973-2979.

DOURSON, M. J., and STARA, F. J. 1983. Regulatory history and experimental support of uncertainty (safety) factors. Reg. Tox. and Pharm. 3:224:238.

FOOD AND DRUG ADMINISTRATION (FDA). 1982. Toxicological principles for the safety assessment of direct food additives and color additives used in food. Bureau of Foods, Washington, D.C.

FOOD SAFETY COUNCIL, SOCIAL AND ECONOMIC COMMITTEE. 1979. Principles and processes for making food safety decisions. p. 54.

HOEL, D. G., GAYLOR, D. W., KIRSCHSTEIN, R. L., SAFFIOTTI, V., SCHNEIDERMAN, M. 1975. Estimation of risks of irreversible, delayed toxicity. Journ. Tox. Env. Hlth. 1:133-151.

HOLLSTEIN, M., et. al. 1979. Short-term tests for carcinogens and mutagens. Mutat. Res. 65:133-266.

MANTEL, N., and BRYAN, W. R. 1961. Safety testing of carcinogenic agents. J. Natl. Cancer Inst. 27:455-470.

McCANN, J. 1975. Detection of carcinogens as mutagens in the salmonella/microsome test: Assay of 300 chemicals. Proc. Nat. Acad. Sci. 72:5135-5139.

MILLER, J. A., and MILLER, E. C. 1971. Perspectives on the metabolism of chemical carcinogens. In Environmental Carcinogenesis, Emmelot and Kriek (eds) Amsterdam: Elsevier/North Holland Biomedical Press.

NATIONAL ACADEMY OF SCIENCES (NAS). 1982. Risk and decision making: Perspectives and research. National Academy Press, Washington, D.C.

NATIONAL RESEARCH COUNCIL (NRC). 1977a. Drinking water and health—Volume 1. National Academy Press, Washington, D.C.

NATIONAL RESEARCH COUNCIL (NRC). 1977b. Principles and procedures for evaluating the toxicity of household substances. National Academy Press, Washington, D.C.

NATIONAL RESEARCH COUNCIL (NRC). 1978. Saccharin: Technical assessment of risks and benefits. National Academy Press, Washington, D.C.

NATIONAL RESEARCH COUNCIL (NRC). 1982. Identifying and estimating the genetic impact of chemical environmental mutagens. National Academy Press, Washington, D.C.

NATIONAL RESEARCH COUNCIL (NRC). 1983. Risk assessment in the federal government: Managing the process. National Academy Press, Washington, D.C.

NATIONAL TOXICOLOGY PROGRAM (NTP). 1979. Annual plan: Fiscal year 1979. Department of Health, Education, and Welfare, Washington, D.C.

NATIONAL TOXICOLOGY PROGRAM (NTP). 1980. Fiscal year 1980 annual plan, publication No. NTP-79-7. Department of Health, Education, and Welfare, Washington, D.C.

OFFICE OF SCIENCE AND TECHNOLOGY POLICY (OSTP). 1984. Chemical carcinogens; Notice of review of the science and its associated principles. Federal Register 49:21594.

OFFICE OF TECHNOLOGY ASSESSMENT (OTA). 1981. Assessment of technologies for determining cancer risks from the environment. U.S. Government Printing Office, Washington, D.C.

Chapter 3

FAUMAN, M. A., and FAUMAN, B. J. 1978. The psychiatric aspects of chronic phencyclidine use: A study of chronic PCP abusers. In: Phencyclidine abuse: An appraisal. National Institute of Drug Abuse (NIDA). Research Monographs no. 21.

FOOD AND DRUG ADMINISTRATION (FDA). 1977. FDA Drug Bulletin. Vol. 7, no. 4 Sept.–Oct., 1977.

FOOD AND DRUG ADMINISTRATION (FDA). 1981. FDA Drug Bulletin. Vol. 11, no. 2, July 1981.

INSTITUTE OF MEDICINE, NATIONAL ACADEMY OF SCIENCES. 1982. Marijuana and health. Report of a study by a committee of the Institute of Medicine, Division of Health Sciences Policy.

LUISADA, P. N. 1978. The phencyclidine psychosis: Phenominology and treatment. In Phencyclidine abuse: An appraisal. National Institute of Drug Abuse (NIDA). Research Monographs no. 21.

NATIONAL INSTITUTE OF DRUG ABUSE (NIDA). 1982. Annual report to Congress on marijuana and health.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH). 1984. Mood disorders: Pharmacologic prevention of recurrences. Consensus Development Conference Program and Abstract.

KESSLER, S. 1980. The genetics of schizophrenia: A review. In Kieth, S. J., and Mosher, L. R., eds. Schizophrenia. U.S. Government Printing Office, Washington, D.C.

WARREN, K. 1977. Critical review of the fetal alcohol syndrome. National Institute of Alcoholism and Alcohol Abuse, Division of Extramural Research.

Chapter 5

BOFFEY, P. 1976. Anatomy of a decision: How the nation declared war on Swine Flu. Science 192:636-641.

DOWDLE, W. R. 1977. The Swine Flu vaccine program. ASM News 5:243-246.

DOWDLE, W. R., and MILLAR, J.D. 1978. Swine Influenza: Lessons learned. Medical Clinics of North America 62:1047-1057.

CENTERS FOR DISEASE CONTROL (CDC). 1980a. Follow-up on toxic shock syndrome: United States. MMWR 29:297-299 (June 27, 1980).

CENTERS FOR DISEASE CONTROL (CDC). 1981. Diptheria, Tetanus, and Pertussis: Guidelines for vaccine prophylaxis and other preventive measures. MMWR 30:392-396, 401-407 (Aug. 21. 1981).

CENTERS FOR DISEASE CONTROL (CDC). 1982. Surgeon general's advisory on the use of salicylates and Reye Syndrome. MMWR 31:289-290 (June 11, 1982).

CENTERS FOR DISEASE CONTROL (CDC). 1984. Supplementary statement of contraindications to receipt of Pertussis vaccine. MMWR 33:169-171 (April 6, 1984).

COOPER, THEODORE. 1976. Sencer "action-memorandum." In Neustadt, R. E., and Fineberg, H. V. The swine flu affair: Decision-making on a slippery disease. Johns Hopkins University Press, Baltimore. Pp. 146-155.

FOOD AND DRUG ADMINISTRATION (FDA). 1982. Food and Drug Administration: Labeling for salicylate-containing drug products; Advance notice of proposed rulemaking. Federal Register 47:57885-57901 (Dec. 28, 1982).

HINMAN, A. R., and KOPLAN, J. P. 1984. Pertussis and Pertussis vaccine: Reanalysis of benefits, risks, and costs. JAMA 251:3109-3113.

KIMBROUGH, R. D., FALK, H., STEHR, P. 1984. Health implications of 2,3,7,8-tetrachlorodibenzodioxin (TCDD) contamination of residential soil. Jrn. Tox. Env. Hlth. 14:47-93.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1983. Criteria for a recommended standard: Occupational exposure to styrene. Publication No. 83-119 (Sept. 1983).

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1981. Occupational safety in grain elevators and feed mills. Division of Safety Research, Morgantown, West Virginia.

SIR INTERNATIONAL. 1982. Quantitative cancer risk assessment for occupational exposure to ethylene dibromide. Prepared for NIOSH, Contract No. 211-82-0014.

THE TOXIC SHOCK SYNDROME. 1982. A conference held Nov. 20-22, 1981, sponsored by the Institute of Medicine, National Academy of Sciences. Annals. Int. Med. 96:871-890.

Chapter 6

KAIDBEY, I. and KLIGMAN, A. 1978. "Photocontact Allergy to 6-Methylcoumarin." Contact Dermatitis 4:277.

Chemical Marketing Reporter, Dec. 11, 1978.

Chapter 7

AMERICAN SOCIETY FOR CLINICAL NUTRITION. 1979. Report of the Task Force on: The evidence relating six dietary factors to the nation's health. Am. J. Clin. Nut. 32:2621-2748.

BAUM, RUDY M. 1984. Genetic engineering engulfed in new environmental debate. Chem. & Engin. News, Aug. 13, 1984. Pp. 15-33.

BEAHRS, O. S., SHAPIRO, S., SMART, C., and McDIVITT, K. W. 1979. Summary report of the Working Group to Review the National Cancer Institute—American Cancer Society Breast Cancer Detection Demonstration Projects. J. Natl. Cancer Inst. 62:647-709.

Ad Hoc Working Group to Develop Radioepidemiological Tables. Draft Report July 1984.

Charter: Ad Hoc Working Group to Develop Radioepidemiological Tables.

Congressional Record-Senate. S15303-S15304 (Dec. 16, 1982).

GORDON, T., CASTELLI, W. P., HJORTLAND, M. C., KANNEL, W. B., and DAWBER, T. R. 1977. High-density lipoprotein as a protective factor against coronary heart disease: The Framingham Study. Am. J. Med. 62:707-714.

KANNEL, W. B., CASTELLI, W. P., GORDON, T., and McCAMARA, P. M. 1971. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: The Framingham Study. Annals Int. Med. 74:1-12.

KANNEL, W. B., McGEE, D., and GORDON, T. 1976. A general cardiovascular risk profile: The Framingham Study. Am. J. Cardiol. 38:46-51.

LIPIDS RESEARCH CLINICS PROGRAM. 1984. The lipid research clinics coronary primary prevention trial results: I. Reduction in incidence of coronary heart disease. JAMA 251:351-364.

LIPIDS RESEARCH CLINICS PROGRAM. 1984. The lipid research clinics coronary primary prevention trial results: II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 251:365-374.

MILEWSKI, ELIZABETH A. Draft report: The NIH Guidelines for research involving recombinant DNA molecules. Office of Recombinant DNA Activities, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

Minutes of June 23, 1983 meeting of the NIH Ad Hoc Committee to Develop Radioepidemiological Tables.

Minutes of Aug. 11, 1983 meeting of the NIH Ad Hoc Committee to Develop Radioepidemiological Tables.

Minutes of Sept. 28 and 29, 1983 meeting of the NIH Ad Hoc Committee to Develop Radioepidemiological Tables.

Minutes of Nov. 21, 1983 meeting of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables.

Minutes of Jan. 16, 1984 meeting of the NIH Ad Hoc Working Group to Develop Radioepidemiological tables.

Minutes of March 15, 1984 meeting of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables.

Minutes of April 20, 1984 meeting of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables.

Minutes of July 12, 1984 meeting of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables.

MULTIPLE RISK FACTOR INTERVENTION TRIAL RESEARCH GROUP. 1982. Multiple risk factor intervention trial: Risk factor changes and mortality rates. JAMA 248:1465-1477.

NATIONAL CANCER INSTITUTE. 1977. Final reports of the National Cancer Institute Ad Hoc Working Groups on mammography screening for breast cancer and a summary report of their joint findings and recommendations. DHEW Publications No. (NIH) 77-1400.

NATIONAL CANCER INSTITUTE. 1978. 1978 NIH/NCI Consensus Development meeting on breast cancer screening. Oncology 35:39-46.

NATIONAL INSTITUTES OF HEALTH. 1978. Guidelines for research involving recombinant DNA molecules. Federal Register 43:60108-60131 (Dec. 22, 1978).

NATIONAL INSTITUTES OF HEALTH. 1978. Recombinant DNA research: Revised guidelines. Federal Register 43:60080-60105 (Dec. 22, 1978).

NATIONAL INSTITUTES OF HEALTH. 1981. Recombinant DNA research: Final plan to assess the risks of recombinant DNA research. 46:30772-30778 (June 10, 1981).

NATIONAL INSTITUTES OF HEALTH. 1979. Recombinant DNA research: Final plan for a program to assess the risks of DNA research. Federal Register 44:53410-53412 (Sept. 13, 1979).

NATIONAL INSTITUTES OF HEALTH. 1982. Program to assess the risks of recombinant DNA research; Proposed second annual update. Federal Register 47:55104-55109 (Dec. 7, 1982).

NATIONAL INSTITUTES OF HEALTH. 1983. Guidelines for research involving recombinant DNA molecules. Federal Register 48:24556-24581 (June 1, 1983).

NATIONAL INSTITUTES OF HEALTH. 1983. Recombinant DNA research; Actions under guidelines. Federal Register 48:1156-1158 (Jan. 10. 1983).

NATIONAL INSTITUTES OF HEALTH. 1983. Recombinant DNA research; Actions under guidelines. Federal Register 48:24548-24553 (June 1, 1983).

NATIONAL INSTITUTES OF HEALTH. 1983. Recombinant DNA research; Actions under guidelines. Federal Register 48:53056-53057 (Nov. 23, 1983).

NATIONAL INSTITUTES OF HEALTH. 1984. Analgesic-associated kidney disease: Conference abstracts.

NATIONAL INSTITUTES OF HEALTH. 1984. Analgesic-associated kidney disease: Consensus development conference statement.

NATIONAL INSTITUTES OF HEALTH. 1984. Recombinant DNA research; Actions under guidelines. Federal Register 49:17844-17848 (April 25, 1984).

NATIONAL INSTITUTES OF HEALTH. 1984. Research in prevention: Fiscal years 1981-1983 (1984 estimated).

NATIONAL INSTITUTES OF HEALTH. 1985. Report of the National Institutes of Health Ad Hoc Working Group to develop radioepidemiological tables. NIH publication no. 85-2748 (Jan. 1985).

NATIONAL INSTITUTES OF HEALTH, RECOMBINANT DNA ADVISORY COMMITTEE. 1982. Minutes of meeting: Oct. 25, 1982.

NATIONAL INSTITUTES OF HEALTH, RECOMBINANT DNA ADVISORY COMMITTEE. 1984. Minutes of meeting: Feb. 6, 1984.

NATIONAL RESEARCH COUNCIL, ASSEMBLY OF LIFE SCIENCES, COMMITTEE ON DIET, NUTRITION, AND CANCER. 1982. Diet, Nutrition, and Cancer. National Academy Press, Washington, D.C.

PERRY, S. 1978. Statement on recommendations of the Consensus Development Panel on breast cancer screening. J. Natl. Cancer Inst. 60:1523-1524.

RAAB, C., and TILLOTSON, J. L., eds. Heart to heart: A manual on nutrition counseling for the reduction of cardiovascular disease risk factors. U.S. Department of Health and Human Services, National Institutes of Health. NIH Publication No. 83-1528.

STAMLER, J. 1978. Lifestyles, major risk factors, proof and public policy. Circulation 58:3-19.

SUN, MARJORIE. 1984. Biotechnology's regulatory triangle. Science 225:697-698.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, THE SECRETARY OF HEALTH AND HUMAN SERVICES. 1982. Charter: Recombinant DNA Advisory Committee. June 24, 1982.

Chapter 8

ANNEST, J. L., PIRKLE, J. L., MAKUC, D., NEESE, J. W., BAYSE, D. D. and KOVAR, M. G. 1983. Chronological trends in blood lead levels between 1976 and 1980. N. Engl. J. Med. 308:1373-77.

MAHAFFEY, K. R., ANNEST, J. L., ROBERTS, J. and MURPHY, R. S. 1982. National estimates of blood lead levels: United States 1976-1980. N. Engl. J. Med. 307:573-579.

NATIONAL CENTER FOR HEALTH STATISTICS. 1983. Health, United States, 1983. DHHS Pub. No. (PHS) 84-1232. Public Health Service. Washington, D.C. U.S. Government Printing Office (Dec. 1983).

NATIONAL INSTITUTES OF HEALTH. 1983. Liver transplantation. Consensus Development Conference Summary. Vol. 4, No. 7.

NATIONAL TOXICOLOGY PROGRAM. 1983. Carcinogenesis bioassay of pentachloroethane (CAS No. 76-01-7) in F344/N rats and B6C3F1, mice (gavage study). NIH Pub No. 83-1788. (April 1983).

NATIONAL TOXICOLOGY PROGRAM. 1984. Annual plan: Fiscal year 1984. Department of Health, Education, and Welfare, Washington, D.C.

OFFICE OF HEALTH RESEARCH, STATISTICS, and TECHNOLOGY. 1982. Public Health Service assessment of percutaneous transluminal angioplasty for treatment of stenotic lesions of a single coronary artery. Vol. 2, no. 16.

OFFICE OF HEALTH TECHNOLOGY ASSESSMENT. 1983. Public Health Service procedures for evaluating health care technologies for purposes of medicare coverage.

PICHLMAYR, R. 1983. Consensus development conference on liver transplantation: Experience with liver transplantation. Hanover Press.

RUUD, A. F. K., and GIPS, C. H. Skills and resources. Department of Surgery and Internal Medicine, University Hospital Groningen, The Netherlands.

SCHARSCHMIDT, B. F. Collation of data on human liver transplantation from four centers. Dept. of Medicine and Liver Center, Univ. of California, San Francisco.

SURGEON GENERAL. 1984. Passive smoking. In The Health Consequences of Smoking—Chronic Obstructive Lung Disease.

VAN THIEL, D. H., SCHADE, R. R., HAKALA, T. R., STARZL, T. E., and DENNY, D. Liver procurement for orthotopic transplantation: An analysis of the Pittsburgh experience. Depts. of Medicine and Surgery and the Transplant Foundation of Pittsburgh, Univ. of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

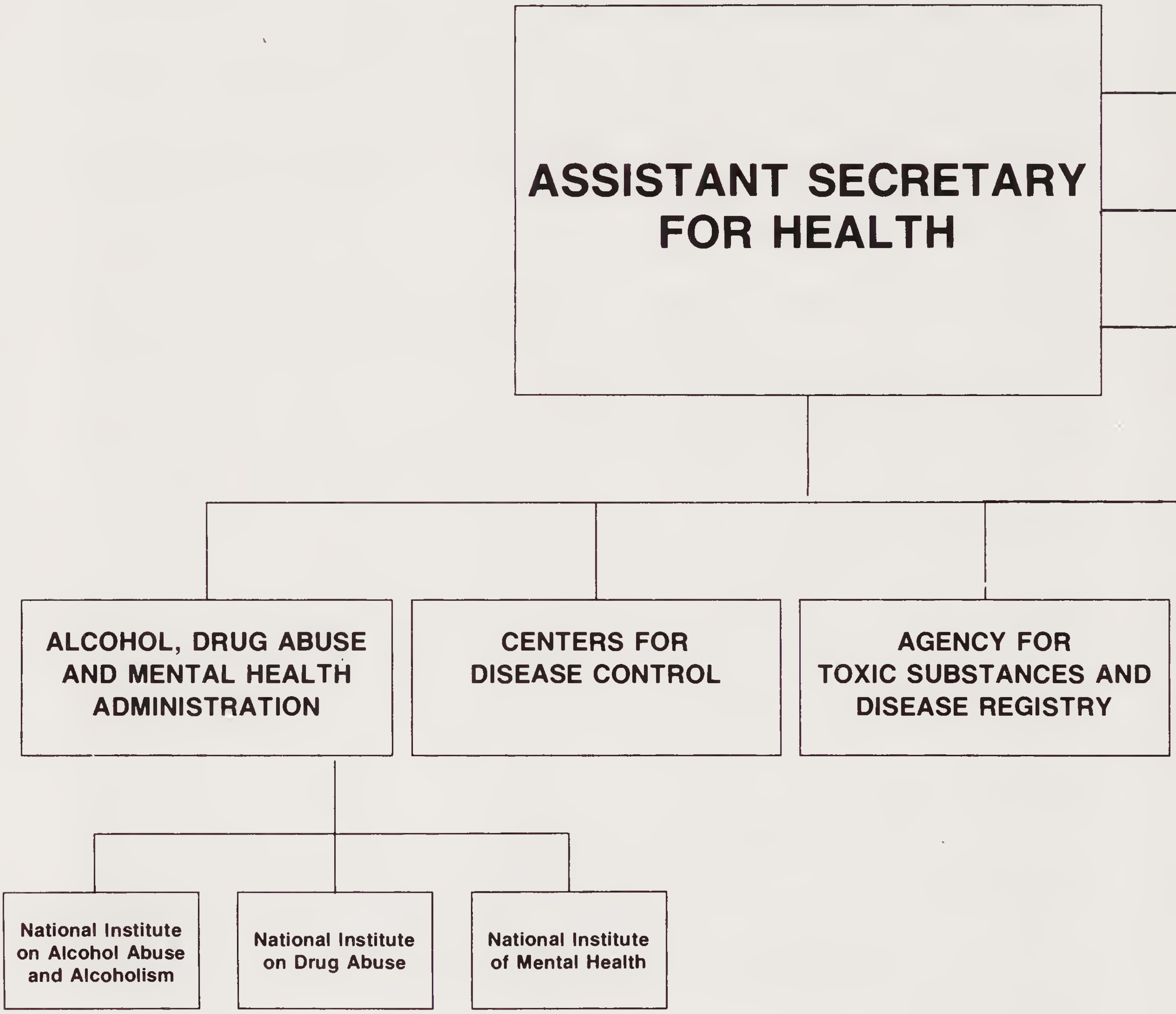
VIERLING, J. M. Epidemiology and clinical course of liver diseases: Identification of candidates for heptic transplantation. Univ. of Colorado School of Medicine, Denver, Colorado.

WALDO, D. R. 1982. Health care financing trends. Health Care Financing Administration, Bureau of Data Management and Strategy. Vol. 3, no. 1.

Chapter 9

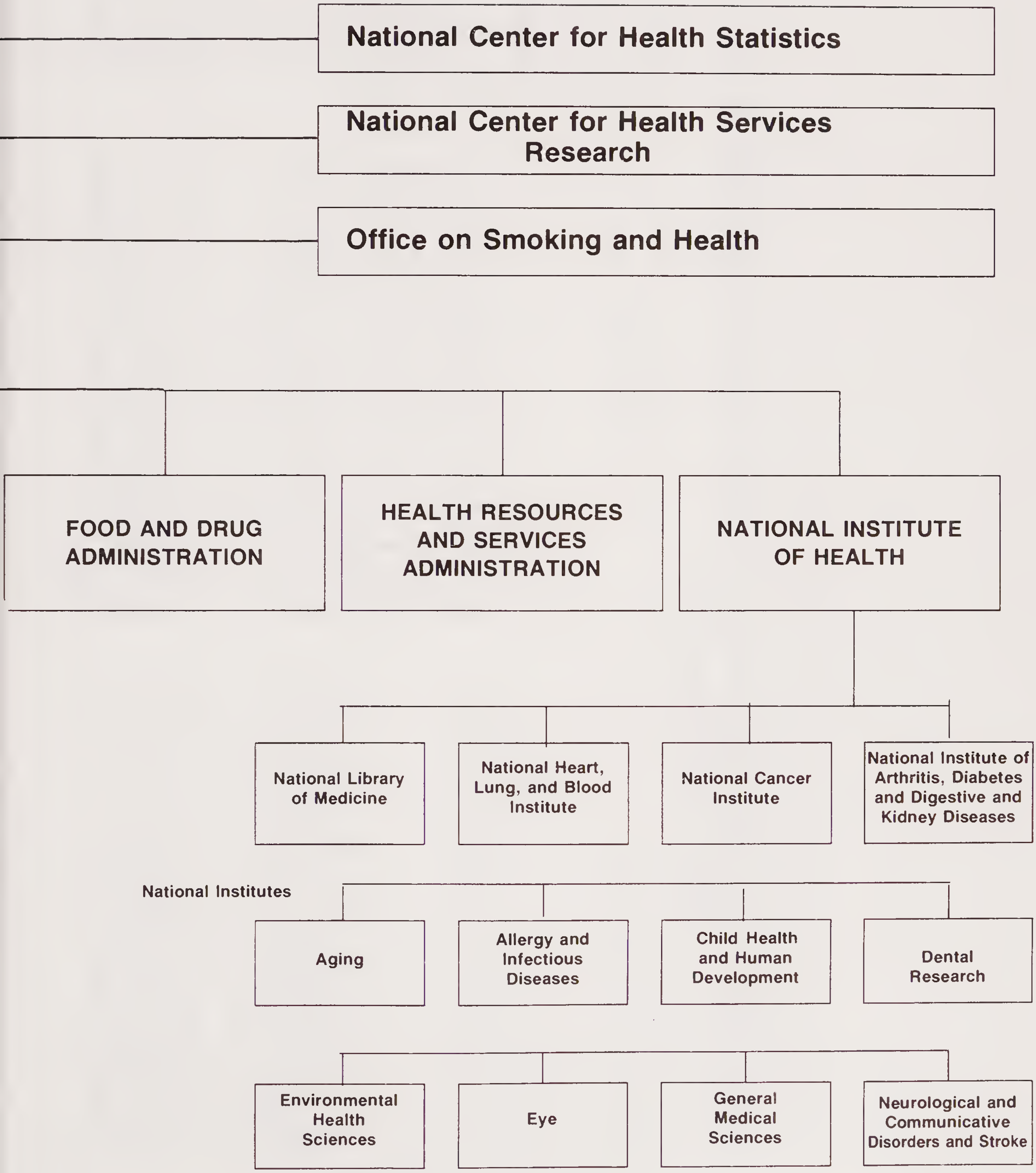
NATIONAL RESEARCH COUNCIL (NRC). 1984. Toxicity testing: Strategies to determine needs and priorities. National Academy Press, Washington, D.C.

Appendix 4: ORGANIZATION CHART OF THE PUBLIC HEALTH SERVICE


ASSISTANT SECRETARY FOR HEALTH
ALCOHOL, DRUG ABUSE AND MENTAL HEALTH ADMINISTRATION
CENTERS FOR DISEASE CONTROL
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY
National Institute on Alcohol Abuse and Alcoholism
National Institute on Drug Abuse
National Institute of Mental Health

OASH Programs

- National Toxicology Program
- Committee to Coordinate Environmental and Related Programs


National Center for Health Statistics
National Center for Health Services Research
Office on Smoking and Health
FOOD AND DRUG ADMINISTRATION
HEALTH RESOURCES AND SERVICES ADMINISTRATION
NATIONAL INSTITUTE OF HEALTH
National Library of Medicine
National Heart, Lung, and Blood Institute
National Cancer Institute
National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases
National Institutes
Aging
Allergy and Infectious Diseases
Child Health and Human Development
Dental Research
Environmental Health Sciences
Eye
General Medical Sciences
Neurological and Communicative Disorders and Stroke

Appendix 5: COMPARISON OF COMPONENT STEPS IN HEALTH RISK ASSESSMENT

NRC (1983)*	*TFHRA** (1985)*	*CCERP*** (1985)*
		Risk: The probability of an adverse health effect as a result of exposure to a hazardous substance(s).
	Risk Assessment: The qualitative or quantitative estimation of the likelihood of adverse effects from exposure to specified health hazards or from the absence of beneficial influences.	*Risk Assessment:* The use of available information to evaluate and estimate exposure to a substance(s) and its consequent adverse health effects. Risk assessment consists of one or more of the following four elements:
Hazard identification: The determination of whether a particular chemical is or is not causally linked to particular health effects.	*Hazard identification:* The qualitative indication that a substance/condition may adversely affect human health.	• *Hazard identification:* The qualitative evaluation of the adverse health effects of a substance(s) in animals or in humans.
Dose-response assessment: The determination of the relation between the magnitude of exposure and probability of occurrence of the health effects in question.	*Hazard characterization:* The qualitative and quantitative evaluation of the nature of the adverse effects, including their expression as functions of the amount of exposure (dose).	• *Dose-response assessment:* The process of estimating the relation between the dose of a substance(s) and the incidence of an adverse health effect.

Exposure assessment: The determination of the extent of human exposure before or after application of regulatory controls.	*Exposure characterization:* The qualitative and quantitative evaluation of the degree of human exposure likely to occur.	• *Exposure assessment:* The evaluation of the types (routes and media), magnitude, time, and duration of actual or anticipated exposures and of doses, when known; and, when appropriate, the number of persons who are likely to be exposed.
Risk characterization: The description of the nature and often the magnitude of human risk, including attendant uncertainty.	*Risk determination:* The integration of these steps into a scientific determination of the level of risk as a basis for policy consideration.	• *Risk characterization:* The process of estimating the probable incidence of an adverse health effect to humans under various conditions of exposure, including a description of the uncertainties involved.
Risk management: The process of evaluating alternative regulatory actions and selecting among them.		*Risk management:* The process of integrating risk-assessment results with engineering data and social, economic, and political concerns, then weighing alternatives to select the most appropriate public health action, ranging from public education to interdiction, that will lead to reduction or elimination of the identified risk.

**NRC (1983):* Risk Assessment in the Federal Government: Managing the Process National Research Council (NRC), National Academy Press, 1983.
***TFHRA (1985):* Determining Risk—Report of the Task Force in Health Risk Assessment (TFHRA), Department of Health and Human Services, 1985.
****CCERP (1985):* Risk Assessment and Risk Management of Toxic Substances. A report to the Secretary, DHHS, from the Executive Committee, DHHS Committee to Coordinate Environmental and Related Programs (CCERP), April 1985.

Appendix 6

RISK ASSESSMENT AND RISK MANAGEMENT OF TOXIC SUBSTANCES

A Report to the Secretary

Department of Health and Human Services (DHHS)

from the

Executive Committee

DHHS Committee to Coordinate Environmental and Related Programs (CCERP)

April 1985

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

May 23, 1985

A professor of philosophy has written, "The question in human action is never the indefinite one of whether to accept risk or not . . . the question can only be whether to accept this risk or that one."

All of us are risk-takers. We take chances in nearly every one of our daily activities—going from place to place, engaging in sports and hobbies, operating machines and equipment. Consciously or unconsciously, we weigh the benefits of each activity against the risks we perceive, and we make informed choices.

Other risks that we may confront are not well known or well understood, either by the lay public or, in many cases, by the scientific community itself. It is these risks that provide the greatest challenge for those having responsibility for risk assessment and risk management decisions. It is also these risks that provide the greatest level of concern for the public. This subset of risk is created primarily by exposure to toxic substances.

I asked for this report of my Department's Committee to Coordinate Environmental and Related Programs to help government officials make more effective public policy regarding risk management, and to help all of us make more informed decisions. It is a first step toward developing a problem-solving approach to risk assessment that will serve both policymakers and the American public.

Risk assessment will remain a national concern as long as our society continues to advance. Through research and open discussion, we can assure that decisions are made intelligently, democratically, and fairly.

Margaret M. Heckler

Margaret M. Heckler
Secretary

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In this effort, the group drew on the expertise of senior scientists from CDC, FDA, and NIH and formed the Task Force on Risk Assessment and Risk Management.

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SECTION 1: PREFACE

This report was prepared at the request of the Secretary, Department of Health and Human Services (DHHS), who asked for a review of the Department's efforts in risk assessment and risk management of substances with toxic effects. The Executive Committee, Committee to Coordinate Environmental and Related Programs (CCERP) of DHHS, was directed to analyze "all DHHS programs in toxicology research, scientific risk assessment, and risk management, with several goals: a) defining a single philosophy of risk and what the Department should do about it; b) describing the most common assumptions upon which risk assessment is based; and c) developing in concept a problem-solving approach toward risk management." A copy of the Secretary's memorandum is in the Appendix (Subsection 12.1).

Because the Secretary's request specifically referred to substances with toxic effects—not agents that have toxic effects, accordingly all physical agents were excluded from consideration. Similarly, the definitions developed for use in this report concern, specifically, substances that have toxic effects. However, the general concepts discussed may be relevant for other issues that come before the department.

In response to the Secretary's request, the Executive Committee, CCERP, established a Task Force on Risk Assessment. The Task Force was staffed with persons from three agencies represented on CCERP's Executive Committee: the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH). The CDC members were from the Center for Environmental Health (CEH) and the National Institute for Occupational Safety and Health (NIOSH); the FDA members were from the National Center for Toxicological Research (NCTR) and the Center for Food Safety and Applied Nutrition (CFSAN); and the NIH members were from the National Institute of Environmental Health Sciences (NIEHS).

In developing the information base for the Secretary, the Task Force found that much had been published recently on risk assessment and risk management. Two reports with background information on risk assessment and risk management were particularly useful: the National Academy of Sciences (NAS) *Risk Assessment in the Federal Government: Managing the Process* (1983) (1) and the Office of Science and Technology Policy (OSTP) *Chemical Carcinogens: A Review of the Science and Its Associated Principles* (1984) (2). The purpose of this Report, therefore, was to supplement existing reports rather than start anew. It is intentionally terse and is not meant to be all-inclusive. Moreover, it is restricted to risk assessment and risk management only as these activities pertain to DHHS.

Given the time constraints, it was not possible for the Task Force to survey and thoroughly analyze the DHHS programs in toxicology, risk assessment, and risk management. As a substitute measure, the Task Force surveyed Public Health Service (PHS) agencies by using a written questionnaire to determine their roles and the resources related to risk assessment and risk management. The reader is cautioned that the questions were not subject to pretesting because of the time constraints and, therefore, questions were interpreted differently by different organizational units. An analysis of products from the survey, reviews of articles and reports on risk analysis, and the personal experiences of Task Force and CCERP Executive Committee members (or their representatives) influenced how this Report was prepared. The reader should consider the definitions in the next section (Section 2: Definition of Terms) before reading the rest of the Report. The definitions and the background statement on how they were developed are essential to an understanding of the Report. Section 3 is an Executive Summary.

The main part of the Report begins with a background section (Section 4). A brief review of the biologic effects of toxic substances and the public's concern with these effects is given; this is followed by brief descriptions of units within PHS with major responsibilities in risk assessment and management of chemicals with toxic effects and a review of causes for some of the problems in risk management. Section 5 contains an overview of some of the information provided by the agencies in response to the survey questionnaire. The data in the questionnaire may have been provided in some instances with considerable uncertainty about how to categorize specific activities in toxicology, risk assessment, or risk management.

Other sections of the Report contain a discussion of important components of risk, culminating in a proposal for a DHHS philosophy of risk (Section 6). This is followed by a discussion of the assessment of risk and the assumptions and uncertainties therein (Section 7). The management of risk comprises the basis of Section 8. One suggested problem-solving approach to risk management is contained in Section 9, which consolidates and extends the material in Sections 7 and 8. Section 10 contains recommendations for administrative actions and scientific research that the Task Force believes would improve risk-assessment and risk-management processes. Section 11 contains the references, while the Appendix, Section 12, contains some materials referred to in the Report.

James O. Mason, M.D., Dr.P.H.
Assistant Surgeon General
Chairman, Executive Committee,
Committee to Coordinate
Environmental and Related Programs

SECTION 2: DEFINITION OF TERMS

2.1 DERIVATION OF DEFINITIONS

For clarity and a better understanding of the Report, key definitions are presented in the next part of this section. The definitions were influenced particularly by those in two key resource documents (1,2). When appropriate, differences between the definitions in the Glossary in this Report and the corresponding terms in the two documents are described. In addition, the questionnaire survey (Subsection 12.2) of agencies involved in risk assessments and risk-management actions asked for information concerning definitions of terms. Of the 26 units surveyed, seven suggested changes in some or all of the definitions in the Glossary. These changes were adopted in part, or wholly, when they were considered by the Task Force to be an improvement.

The definition of "risk" includes the concept of probability of harm (3), which, in this Report, is an adverse health effect from toxic substances.

The definition of "risk assessment" and its four elements are modifications of definitions in the National Academy of Sciences (NAS) (1) and Office of Science and Technology Policy (OSTP) (2) documents. The definition of risk assessment used in this Report corresponds to the NAS definition, with minor changes in wording. The NAS and OSTP documents both agree on the four components in a risk assessment: hazard identification, exposure assessment, dose-response assessment, and risk characterization.

The definition of "hazard identification" is modeled on the OSTP definition. It is more general, however, in that it refers to a number of toxic effects rather than carcinogenesis alone. The definition of "exposure assessment" also follows the OSTP definition, but includes the words "exposure" and "dose." "Exposure" refers to the level or amount of chemical presented to the subject at risk; "dose" refers to the amount administered or the level of the chemical that is biologically effective. The definitions of "dose-response assessment" and "risk characterization" are minor modifications of the corresponding NAS definitions.

The definition for "risk management" merits special comment. The OSTP document does not refer to this term. The NAS document defines risk management as "the process of weighing policy alternatives and selecting the most appropriate regulatory action, integrating the results of risk assessment with engineering data and with social, economic, and political concerns to reach a decision." This definition, which restricts risk management to regulatory actions, was broadened to cover the full range of actions in risk management. Once a health hazard from a toxic substance has been identified, regulatory action may be considered to abate the risk. That, clearly, is one possibility—one that depends on specific applicable legislative authorization. In addition, when permitted by statute, DHHS units may take other actions that contribute to the control or elimination of an identified risk. Examples are: issuing public health advisories, conducting public education programs, and collaborating with other government agencies and the private sector.

2.2 GLOSSARY OF TERMS

RISK—The probability of an adverse health effect as a result of exposure to a hazardous substance(s).

RISK ASSESSMENT—The use of available information to evaluate and estimate exposure to a substance(s) and its consequent adverse health effects. Risk assessment consists of one or more of the following four elements:

- HAZARD IDENTIFICATION—The qualitative evaluation of the adverse health effects of a substance(s) in animals or in humans.

- EXPOSURE ASSESSMENT—The evaluation of the types (routes and media), magnitudes, time, and duration of actual or anticipated exposures and of doses, when known; and, when appropriate, the number of persons who are likely to be exposed.

- DOSE-RESPONSE ASSESSMENT—The process of estimating the relation between the dose of a substance(s) and the incidence of an adverse health effect.

- RISK CHARACTERIZATION—The process of estimating the probable incidence of an adverse health effect to humans under various conditions of exposure, including a description of the uncertainties involved.

RISK MANAGEMENT—The process of integrating risk-assessment results with engineering data and social, economic, and political concerns, then weighing alternatives to select the most appropriate public health action, ranging from public education to interdiction, that will lead to reduction or elimination of the identified risk.

Other important factors in understanding risk are defined throughout the document, for example, the acceptability of risk and relative risk are discussed in Subsection 6.3.

SECTION 3: EXECUTIVE SUMMARY

The Secretary, Department of Health and Human Services (DHHS), requested the chairman of the Executive Committee, Committee to Coordinate Environmental and Related Programs (CCERP), to analyze the Department's programs in toxicology research, scientific risk assessment, and risk management in order to define a single philosophy of risk, describe the most common assumptions used in risk assessment, and develop a problem-solving approach to risk management. The Executive Committee, CCERP, appointed a group with representatives from the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH) to develop a response. The group drew from the expertise of senior scientists in the various Public Health Service (PHS) agencies. Because the subject of the memorandum from the Secretary was the risk management of toxic substances, the group limited discussion to that topic. However, the general concepts discussed may be relevant for other issues that come before the Department.

To set the stage for the specific responses to the Secretary, the body of the Report opens with a background section. The first subsection concerns the biologic and toxic effects of substances. Human exposure to substances with toxic effects occurs in the workplace and in the community environment. Several biologic effects that are of concern to the public may result from exposure to toxic substances, including cancer, reproductive problems, genetic effects, clinical effects, and subclinical effects. Both epidemiology and toxicology contribute to estimating the biological effects, and both disciplines have strengths and limitations. Several general principles from these two disciplines are relevant to risk assessment—for example, in epidemiology, full knowledge of etiologic factors is not required for effective control; in toxicology, the effects produced by chemicals in animals, when properly qualified, are applicable to humans. The second subsection deals with public concerns about the toxic effects of chemicals. These concerns can be characterized as the concerns of individuals about adverse health effects, the effective control of hazardous substances, and the scientific bases of the processes of assessing and managing risks.

As part of the background, a brief subsection on history is followed by another brief one on the present activities of PHS agencies and some of the organizational units in those agencies. This overview is focused on risk-assessment/risk-management activities. It appears that DHHS is an amalgam of units with different responsibilities in risk assessment and risk management. Levels of involvement also vary, on the basis of each particular unit's legislative history and present statutory requirements. The involvement can range from doing research to identify hazards through the direct control of the hazards. Many PHS units perform some risk-assessment and risk-management activities. The Report describes the Department's role.

In an effort to analyze some of these activities further, a questionnaire was sent to the PHS units thought to be involved in risk assessment and risk management. Because of the restricted time frame, the questionnaire was mailed out (limiting interaction of the respondents with the preparers), and the time for the agencies to prepare their replies was very short. However, the results, although qualified, can be used to make some general statements—for instance, that all PHS agencies surveyed are involved in risk assessment activities.

Section 6 is directed to the first part of the Secretary's request, that is, to define a philosophy of risk. Defining a single philosophy of risk was difficult in the light of differences in the legislation pertinent to DHHS units. In coping with these difficulties, six concepts were useful in formulating a philosophy of risk: statutory concerns, acceptability of risk, estimation of risk, voluntary aspects of risk, perception of risk, and processes of risk assessment and risk management. With a philosophy defined as a set of motivating concepts or principles, the philosophy of risk developed for this Report is:

> Individuals have always lived with risk, presently live with risk, and will continue to live with risk in the future. Some degree of risk of adverse health effects from toxic substances is inevitable, as a consequence of exposure to both naturally occurring and manmade toxicants. The public should be made aware of the nature of the risk. Public health risks that are not acceptable should be reduced or eliminated when feasible. Means to accomplish this goal should not pose additional significant risks.

Some specific actions to be considered when putting this philosophy into practice are described in detail.

The section on the common assumptions used in risk assessment begins with a discussion of the four steps involved in risk assessment - hazard identification, exposure assessment, dose-response assessment, and risk characterization. The strengths and limitations of the data involved in each step are considered, and the primary assumptions most commonly employed in the process are briefly reviewed. Because of the history of methodological development, a good deal of emphasis is placed on risk assessment for carcinogenesis, although other endpoints such as mutagenesis and teratogenesis are considered. The discussion of dose-response assessment includes descriptions of the safety-factor approach, the margin-of-safety approach, and mathematical modeling. Two examples of commonly used assumptions in risk assessment are that 1) an appropriately chosen dosage scale allows for the extrapolation of observed experimental results across species, and 2) average doses give a reasonable measure of exposure when dose rates are not constant in time. In the Report, special emphasis is placed on dealing with uncertainties in risk assessment.

To set the stage for the problem solving approach to risk management, Section 8 discusses risk-management activities across the Department in a general context, with an emphasis on factors that tend to be important for more than one agency. Some of the major issues in risk management are also discussed: communicating to the public the nature of risks; appropriate identification of scientific uncertainties; shared responsibilities for risk-benefit decisions; peer review; adequate delineation of policy and science; and continuing evaluation of activities.

Section 9 contains the problem-solving approach requested by the Secretary. The major challenge in risk management is to enhance public welfare through effectively managing the risks of a chemical that has toxic effects under practical conditions of use and exposure. Agencies now effectively address problems when they arise. This problem-solving approach attempts to facilitate this process systematically. It looks at risk management in an integrated fashion, using a framework which includes an analysis of the risk assessment, an analysis of possible options, the promotion of the understanding and acceptance of risk-management decisions, and the evaluation of the effectiveness of the options chosen. Use of this framework allows a systematic approach to resolving the difficulties that arise in making risk-management decisions. Also, an attempt is made to incorporate as much of the scientific method into the process of risk management as possible. Although different from the classical paradigm used in problem solving, this approach emphasizes that each risk management, besides addressing issues in public health, can also be seen as an example of a solution to a complex problem, from which we can learn. Applications of this approach are illustrated.

The Report concludes with recommendations for administrative and research efforts that would improve the science involved in risk assessment and risk management.

SECTION 4: BACKGROUND

4.1 BIOLOGIC EFFECTS OF TOXIC SUBSTANCES

Background material is presented here, in a very brief form, on the (not mutually exclusive) biologic and toxic effects of substances on human health and on some of the principles of epidemiology and toxicology relevant to the study of toxic substances (also not mutually exclusive). For further information, the reader is referred to standard textbooks on toxicology (4), environmental medicine (5), and epidemiology (6).

Human exposure to naturally occurring and manmade toxicants found in the workplace and community environments has resulted in biologic effects. Some biologic effects are understood as being adverse health outcomes; others are more difficult to relate to overt health effects. Some of the adverse health outcomes have been known since antiquity, for instance, the fatal effects of lead poisoning. The significance to health of other biologic outcomes, like subtle changes in enzyme systems, is uncertain. The effects of toxic substances, therefore, can range from subtle biologic changes to frank clinical effects. A general grouping of the biologic effects of known toxicants, with examples of the human health effects of select ones, and comments on the relevance to risk assessment are as follows:

Cancer—There are environmental substances which have been found to induce some types of cancer in humans. Classes of toxicants in the environment that can cause cancer are naturally occurring substances, (for example, aflatoxin), naturally occurring and waste metals (for example, chromium, nickel), chlorinated hydrocarbons (for example, vinyl chloride), mineral fibers (for example, asbestos), and complex mixtures of chemical compounds (for example, tobacco smoke). Cancer is an adverse health outcome of major concern to the public and has, therefore, been the focus of many risk assessments.

Reproductive Problems—Some substances have the capacity to cause adverse human reproductive effects, including infertility, miscarriage, and defects in the fetus. Some substances that can cause reproductive effects are metals (for example, lead, methyl mercury), pesticides (for example, dibromochloropropane), and drugs (for example, thalidomide). Like cancer, adverse reproductive health consequences are of major concern to communities and health officials. Several government agencies have conducted qualitative risk assessments on reproductive toxicants. Quantitative assessments in this area have been based primarily on the safety-factor approach.

Genetic Effects—Some substances cause changes in the DNA, the basic genetic material of life. The health significance of these effects is not clear. The scientific debate continues on whether the toxic effects on genetic material may lead to cancer or adverse reproductive outcomes, a possibility that also generates public concern. Qualitative risk assessments on substances based on their genetic toxicity, have not been common (one example is ethylene oxide), but are likely to increase as concern deepens. Quantitative risk assessments in this area have also been few.

Clinical Effects—In addition to the endpoints mentioned above, specific tissues can be affected by certain substances. These "target" tissues may include any part of the body, for example, lungs, heart, liver, kidneys, nervous system (and psychologic state), and skin. The health consequences can range in severity from loss of function (for example, kidney failure due to heavy-metal intoxication) to less severe effects (like chloracne). Risk assessments focused on these clinical effects have usually been qualitative.

Subclinical Effects—Some biologic effects of substances are not manifested as overt clinical events; these may be subtle changes in enzyme systems, irritation of sensory tissue, or changes in psychologic state, which can be termed subclinical. As with clinical effects, subclinical health effects have been included only in qualitative risk assessments.

The possible biologic effects on humans are determined by the specific chemical to which a person is exposed, by the duration and the frequency of exposure, by the route of exposure, by the presence of other chemicals in the exposure, and by subject-specific factors. Toxic effects, which may be acute (short duration) or chronic (persistent), may be produced by exposures that are acute and/or chronic (these are separate classes; for example, a chronic effect can be caused by an acute exposure). Acute exposure can be either a single exposure or multiple exposures within a short time. Often, the toxic effects of acute exposure are quite different from those of chronic exposure. Important subject-specific factors include a person's age, sex, health status, and diet. All factors that may influence the health effect resulting from exposure to a toxic substance are important in the assessment and management of risk. Although many scientific disciplines in biology and medicine are in some way involved in hazard identification, epidemiology and toxicology are the two of greatest importance in determining the biologic effects of toxic substances.

4.1.1 Principles of epidemiology relevant to risk assessment

Epidemiology is the study of the distribution and determinants of diseases and injuries in human populations (6). It is concerned with the frequencies and kinds of illnesses and injuries in groups of people and with the factors that determine or otherwise influence their distribution. Epidemiologic data, by virtue of their direct relevance to humans, are compelling in any risk assessment.

The following basic principles are often relevant to risk assessment of hazardous chemicals:

- Epidemiology provides the means for investigating the health effects of chemicals directly in humans under conditions of actual exposure, avoiding a need for interspecies extrapolation.
- Epidemiologic observations can only be made after people have been exposed.
- Inferences can be made of the causal relationship between exposure and health effects, provided there is an adequate study design and an effective control of confounding factors.
- Many epidemiologic studies allow an evaluation of the relationship between the magnitude of exposure and the frequency or severity of health effects. (The quality of exposure data is sometimes insufficient for an adequate quantitative dose-response assessment, when they have to be obtained retrospectively.)

4.1.2 Principles of toxicology relevant to risk assessment

Toxicology is the study of the adverse effects of chemicals on living organisms. Three principles of toxicology (4) are currently of special importance in risk assessments:

- The dose-response relationship is the association between the dose of a toxic substance and/or the frequency or severity of biologic effects, and is a fundamental and pervasive concept in toxicology. (In general, as an absorbed dose is increased, the frequency and/or severity of the biologic effects increase.)
- The effects produced by a chemical toxicant in laboratory animals, when properly qualified, are applicable to humans. (Extrapolating results from acute and chronic animal studies is difficult, but experience has shown that toxicology studies in which appropriately chosen animal models are used as surrogates for humans provide data that may be predictive of many human health outcomes.)
- Exposure of experimental animals to high doses is a necessary and valid method of discovering possible hazards to humans. (This principle should not be interpreted as advocating only high doses.)

4.1.3 Principles in the practice of risk management

In applying scientific information from human and animal studies in the conduct of risk management, two principles need to be emphasized:

- Identifying risk factors for an adverse health effect is highly desirable. However, full knowledge of etiology is not necessary for developing effective control measures. (A typical example of this principle in practice is the lowering of blood lead levels by removal of leaded gasoline. The epidemiologic evidence supports a direct causal relationship between lead and a number of toxicological endpoints, although the precise toxic mechanisms are not fully understood.)
- Any proposed measure for controlling adverse health effects should be evaluated in terms of all the effects the measure is likely to have.

4.2 PUBLIC CONCERNS ABOUT TOXIC SUBSTANCES

The public concerns about toxic substances can be categorized as:

a) Concerns of individuals about the health effects of toxic chemicals;

b) Concerns of individuals, communities, and organizations about the activities of industry, and local, State, and Federal governments in the control of hazardous materials and the management of the health risk posed by these substances;

c) Scientific concerns about the appropriateness and correctness of the methods used in assessing the risk of toxic substances.

4.2.1 The public concern about the health effects of exposure

People have a natural desire to live in an environment with a minimum of health risks that are beyond an individual's control and that, thus, is free of imposed risks of the adverse effects of substances with toxic effects. However, the public recognizes that, in practice, some risks are inevitable: toxic metals are naturally present in the earth's crust; many food components contain substances of natural origin that have toxic effects; at present, safe drinking water can only be guaranteed by treating water supplies with chemicals that leave potentially harmful residues; drugs usually have adverse effects that may be harmful; residential and workplace heating is usually inseparable from the production of toxic substances in the atmosphere; living in an industrial society is inseparable from being exposed to manmade chemicals; etc.

4.2.2 The public concern about the control of hazardous materials

In the past decades, the production of new goods and services and the demand for them have increased immensely. Accompanying the manifold benefits of these new products is an increased awareness of the hazards they pose to an individual's health. For the lay public, however, this awareness becomes a vague sense of dread when accompanied by lack of knowledge about factors, such as: a) what toxic chemicals are present and how people can be exposed; and b) who is responsible for the presence of toxic chemicals in the environment and for controlling their presence. The public is aware of the inevitability of some risks, but it also expects that many risks can and should be controlled. The public expects local, State, or Federal governments and industry to manage the risks associated with the toxic effects of chemicals.

Although the public expects the government to act, its response to the consequences of the action may not be positive. For example, individuals with residential exposure usually expect successful risk management to result in elimination of the risk or in a reduction of the risk to levels so low that they do not cause observable health effects. At the same time, they may criticize risk managers if successful control of the risk results in, for instance, a substantial increase in the cost of living. Workers want to be protected from hazards at the workplace, but their reaction to courses of action may often include considerations of unemployment and ability and willingness to comply with individual safety measures. Finally, industrial officers may appreciate having guidelines for the safety of their employees, but may also judge actions on the basis of how they perceive the government regulations will affect the business's ability to survive in a competitive climate.

4.2.3 Scientific concerns

Scientific concerns have been expressed about: a) the relevance to humans of animal studies and in vitro tests in the process of hazard identification; b) the failure of many human studies to adequately identify the hazards and estimate the attendant risks; c) the paucity of facts that often underlie the models used in estimating exposure and risk; and d) the problems and uncertainties inherent in species and dose extrapolation. Scientific concerns have also been expressed that: a) risk-management considerations may have influenced the approach to and the outcome of risk assessment; and b) arbitrariness in decisions on controversial scientific issues has resulted in significant discrepancies in risk assessments and inconsistencies in risk management of the same substance.

In its risk assessment of chemicals in drinking water, the Safe Drinking Water Committee of the National Academy of Sciences highlighted the scientific problems and uncertainties associated with risk assessment (7). As a response to scientific concerns, the Office of Science and Technology Policy (OSTP) has prepared a document (2) that presents the state-of-the-science concerning cancer risk assessment and provides general principles as a basis for guidelines for performing risk assessments.

The National Academy of Sciences (1) has addressed concerns about procedural issues in risk assessment. It suggested that lack of data, not organizational structure, was the fundamental problem in risk assessment. To improve risk assessment, it recommended that:

a) Regulatory agencies take steps to establish and maintain a clear conceptual distinction between risk assessment and risk management;
b) Uniform inference guidelines be developed for use by Federal agencies in the risk-assessment process; and
c) The evolving scientific basis of risk assessment be critically assessed and the recommended inference guidelines be periodically revised accordingly.

The feasibility of risk assessment and risk management is determined by several kinds of constraints. How, and to what extent, an agency may conduct risk assessment or risk management may be dictated by existing statutes and regulations. Scientific knowledge and uncertainties set the limits on what can be done with scientific confidence and where policy judgments have to be made. Finally, technologic and economic considerations may impose practical limitations on risk assessors and risk managers.

4.3 DHHS'S ROLE IN RISK ASSESSMENT AND RISK MANAGEMENT OF TOXIC SUBSTANCES

4.3.1 The history of the organizational units within the Public Health Service

Formed, in 1979, from sections of the Department of Health, Education, and Welfare (DHEW), DHHS is an amalgam of agencies with different historic backgrounds and different coverage of the field of public health. Within DHHS the Public Health Service (PHS) performs the lion's share of risk assessment and risk management of the toxic effects of substances.

PHS, with vastly expanded functions, developed out of the Marine Hospital Service (formed in 1798) and received its present name in 1912. For a number of years, it was part of the Department of the Treasury. Up to the 1920's, its primary function was maintenance of quarantine, which gradually broadened to include other public health functions, such as control of outbreaks of infectious diseases, public sanitation, and the provision of health care to American Indians. These traditional functions can be considered risk management, performed on usually clearly defined health risks. Presently, PHS operates under the much amended PHS Act of 1944, which organized a number of previous PHS Acts containing various functions.

Research has been an important PHS activity since the turn of the 20th century (for example, the conquest of yellow fever). The National Institutes of Health (NIH) evolved from a research branch of PHS that became formalized as an institute in 1930. NIH was moved to Bethesda, Maryland, in 1938 and institutes were added both administratively and by acts of Congress. By 1950, NIH was organized to study the major chronic diseases. Today, it contains 11 institutes, six major divisions, and the National Library of Medicine. NIH supports research in non-Federal institutions and conducts research in its own laboratories and clinics.

The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) was formed in 1973 by the Secretary. It grew from the Division of Mental Hygiene in PHS, created in 1930 to treat narcotic addicts, which evolved into the National Institute of Mental Health (NIMH) in 1946 with the passage of P.L. 487-79, the National Mental Health Act. Centers were established in NIMH for alcoholism and drug abuse in 1966 and they developed into the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (established in 1971 by the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970) and the National Institute on Drug Abuse (NIDA) (established in 1972 by the Drug Abuse Office and Treatment Act). ADAMHA was formed in an effort to focus the effort in addressing the effects of a limited range of toxins—alcohol and abusable drugs.

The Centers for Disease Control (CDC), which grew out of the Communicable Disease Center in 1973, has been the focus for much of PHS's classic public health activity. It presently consists of five centers, three program offices, and one institute, the National Institute for Occupational Safety and Health (NIOSH) NIOSH, which developed from the Bureau of Occupational Safety and Health through the Occupational Health and Safety Act of 1970, has been part of CDC since 1973.

The Food and Drug Administration (FDA) was originally part of the Department of Agriculture; it went through a number of administrative changes, including being part of the Federal Security Agency, before becoming part of PHS in 1968. It was formed in 1906 to guarantee pure food and drugs, but much of its present activity began in 1938, with the passage of the Food, Drug, and Cosmetic Act. It presently consists of five centers.

The Agency for Toxic Substances and Disease Registry (ATSDR) is the youngest agency in PHS. Its basis is in the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or Superfund) of 1980, and it was established in 1983 by an amendment to the PHS Act. It is mandated to study the health effects of hazardous agents on populations living near or at hazardous waste sites.

The Office of the Assistant Secretary for Health (OASH), which administers PHS, has two Centers, two Programs, and one Office that participate in certain risk-assessment and risk-management activities. The National Center for Health Services Research and the National Center for Health Statistics were formed in 1974 and became part of DHEW in 1977. The Committee to Coordinate Environmental and Related Programs, the National Toxicology Program (established in 1978 by the Secretary, DHHS, and granted permanent status in 1981), and the Office on Smoking and Health (OSH) are also in OASH.

4.3.2 Risk-assessment and risk-management activities within DHHS

The PHS Act gives the Secretary broad authority to protect and promote the health of people in the United States. With respect to toxic substances, the Secretary is mandated under Section 301 of the Act to:

1. Support and encourage the conduct and coordination of research relating to the cause, diagnosis, treatment, control, and prevention of diseases in humans;
2. Conduct and support through grants and contracts studies and testing of substances for carcinogenicity, teratogenicity, mutagenicity, and other harmful biologic effects; and
3. Consult with other Federal entities outside the Department engaged in such activities.

Information on some of the organizational units within DHHS was obtained from the survey questionnaire (Subsection 12.2), which requested information on their mandates and missions regarding the assessment or management of risk from toxic chemicals, supplemented by other data. The discussion below is based on this information and is by no means complete or comprehensive.

Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA)—The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is dedicated to research on the mechanisms by which alcohol (ethanol) produces its intoxicating, addicting, and pathologic effects. It is required by the Alcohol and Drug Abuse Act to issue periodically a report on the health effects of alcohol abuse and to disseminate the results of alcohol-related research to various user communities.

The National Institute on Drug Abuse (NIDA) is the lead Federal institute for supporting research directed at improving the understanding of the causes and consequences of drug abuse and the development of improved techniques for preventing drug abuse and treating the abusers. NIDA is involved in developing a data base on the toxicologic effects of abused substances or of drugs intended for the treatment of narcotic addiction.

The National Institute of Mental Health (NIMH) is charged with supporting research to treat and prevent mental disease. NIMH is engaged in risk assessment of toxic substances through its research on the use of psychotherapeutic drugs.

National Institutes of Health (NIH)—Under the authority of the PHS Act, NIH provides leadership and direction to programs designed to improve the health of people in the United States. NIH implements its responsibilities through the conduct and support of research in the cause, diagnosis, prevention, and treatment of diseases of people, which includes the toxicology of environmental contaminants. In addition, it directs programs for the collection, dissemination, and exchange of information on medicine and health.

NIH is organized along categorical lines, with separate institutes devoted to fostering research related to defined portions of the spectrum of human disease. In some cases, institutes are focused on specific diseases or classes of diseases (National Cancer Institute [NCI], National Institute of Allergy and Infectious Diseases [NIAID]). In others, the target is an organ or organ system (National Eye Institute [NEI]; National Heart, Lung, and Blood Institute [NHLBI]), and in still others, a stage in the human life cycle (National Institute of Child Health and Human Development [NICHD], National Institute on Aging [NIA]). Only the National Institute of Environmental Health Sciences (NIEHS) has a specific aim to explore the health effects of chemical substances; all others start with a disease, condition, or disability, and investigate causes, whatever they may be.

As a result of this categorical organization and the mandate to increase understanding and control of disease, research relevant to risk assessment is widely distributed throughout NIH. In almost all instances, however, it is a corollary product of a research activity defined by the outcome health condition, not by the etiologic agent. Research of importance to the field of risk assessment is pursued by the categorical institutes principally as a by-product of two types of investigation. The first is the continuing search for causes of diseases whose etiology is currently not known or poorly understood. The second encompasses the development of new or improved drugs and other forms of treatment for established diseases. No drug is expected to be totally free of adverse effects, and provision for careful monitoring of undesirable side effects is a routine part of study design in the testing and evaluation of all new therapeutic agents. This avenue of research leads to results of rather circumscribed value, however, because the chemical agents used in the pharmacopoeia are ordinarily different from those that are more widely distributed in the environment and are of concern as primary causes of illness in otherwise healthy persons.

NIEHS is primarily involved in the hazard-identification and hazard-characterization steps of risk assessment. Its main emphasis centers on mechanistic studies and their interpretation. It focuses a considerable portion of its resources in research efforts aimed at developing fundamental knowledge of the mechanisms of chemical toxicity and improved techniques for conducting quantitative risk assessments, including the development of biomarkers in laboratory and epidemiological studies, as well as other indicators of biologically effective doses. Through the National Toxicology Program (NTP), NIEHS's involvement in risk management consists primarily of ensuring the dissemination of this information and in providing a scientific resource in this area for consultation with other departmental units and other Federal agencies. NIEHS supports many research projects and research centers at universities and much of the toxicology training in the United States. Many projects involve hazard reduction as well as exposure assessment. Further, in 1980, NIEHS established the Biometry and Risk Assessment Program. This program conducts biochemical, epidemiologic and biomathematical research that is coordinated and directed at developing/improving quantitative methods in risk estimation.

NCI conducts risk-assessment activities, such as epidemiologic studies, to delineate high-risk groups and individuals and to identify occupational and environmental causes of cancer. Examples of hazard-identification activities are: in-vitro studies on mechanisms and host factors that determine susceptibility to carcinogens, research concerning the role of tumor initiators and promoters and cocarcinogens in cancer risk, and combined laboratory and epidemiologic studies of cancer risk. The NCI Carcinogenesis Testing Program, with its resources, was transferred to the NIEHS in 1981. Nevertheless, the NCI maintains a significant level of involvement in the carcinogenesis testing program by nominating chemicals for testing in the bioassay program and by membership on the NTP Executive Committee.

The National Library of Medicine (NLM) provides scientific information for risk assessment of toxic substances by establishing and making accessible data banks on toxicology. These data banks include Toxline, Chemline, the Toxicology Data Bank, and the Hazardous Substances Data Bank.

Centers for Disease Control (CDC) — Under the authority of Section 301 of the Public Health Service Act, CDC conducts research in the health effects of exposure to toxic agents and designs and implements such surveys as may be needed to identify human exposure to these agents. CDC emphasizes the derivation of information on the toxicity of chemicals from studies in humans under conditions of actual exposure. Health studies include responses to emergency situations and long-term systematic or programmatic investigations. All the centers are necessarily involved in the hazard-identification and hazard-analysis parts of risk assessment, but they all go far beyond these steps and intervene directly in the community. This approach is related to the agency's long tradition of close relations with the public and with State and local health authorities.

The Center for Environmental Health (CEH) has a broad mission to conduct investigations, epidemiologic studies, and surveillance programs on environmental hazards as causes of human diseases and on human diseases that may be caused by environmental hazards. In addition, CEH conducts risk assessment and nonregulatory risk-management activities under the National Environmental Policy Act and under interagency agreements with ATSDR and the Environmental Protection Agency (EPA). CEH's priorities for investigations are influenced by requests from private citizens, municipalities, States, and other Federal agencies. CEH evaluates the kind and extent of the health risk imposed by hazardous chemicals that contaminate areas of limited size, residences, or buildings. Other areas of involvement include residential radiation, natural disasters, and the causes of chronic diseases and injuries. CEH emphasizes information generated from epidemiologic studies and exposure surveys.

The National Institute for Occupational Safety and Health (NIOSH) operates primarily under the Occupational Safety and Health Act, the Federal Mine Safety and Health Act, and the PHS Act. It is the Federal organization responsible for research on the health and safety of American workers. NIOSH is a prevention-oriented research institute with goals and objectives in two major areas: 1) conducting research on occupational safety and health issues and producing information on identified problems; and 2) transmitting this information to appropriate parties to protect the worker and control work-related disease and injury. The Institute coordinates its comprehensive research program of laboratory investigations, field surveys, and epidemiologic studies so that appropriate standards and control measures can be recommended. NIOSH is also specifically authorized to recommend standards to the Department of Labor. Formal NIOSH reports include the "Criteria Documents" (which are comprehensive reviews of specific occupational hazards), "Current Intelligence Bulletins" (which contain brief reviews of new information on possible health hazards), and responses to "Regulatory Actions of the Department of Labor" (which present the policy of NIOSH in rule-making efforts). Criteria Documents may be used as a basis for subsequent regulation of the workplace by OSHA. NIOSH is actively involved in toxicological research and participates in the NTP.

Agency for Toxic Substances and Disease Registry (ATSDR)—ATSDR is mandated to carry out its health-related responsibilities under CERCLA (Superfund) and the Resource Conservation and Recovery Act, as amended in 1984. Currently, ATSDR fulfills most of its mandate through interagency agreements with CDC, the Environmental Protection Agency (EPA), NIH, and NTP, and, for specific activities, through cooperative agreements and contracts with States and other organizations. ATSDR's activities comprise determining the extent of health risk to the population from a release or threatened release of a hazardous substance into the ambient environment; establishing registries of diseases and of people environmentally exposed to hazardous agents; establishing a data bank on the toxicity of chemicals; and studying the relation between exposure to toxic agents and illness (including human studies, in-vivo and in-vitro testing, and surveillance systems).

Food and Drug Administration (FDA)—Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), the PHS Act, and six other independent acts, FDA is given the responsibility and authority for ensuring the safety of food, drugs, cosmetics, biologic products, radiation-emitting electronic products, and medical devices that are in interstate commerce. Under the FD&C Act, FDA is required to make decisions on the approval or denial of new products or on the status of existing products. FDA disseminates information, conducts and participates in many of the risk-assessment and risk-management activities discussed above for other agencies. In addition, it has a major regulatory responsibility and uses risk assessment and risk management to meet this responsibility.

The Center for Food Safety and Applied Nutrition (CFSAN) has the responsibility for maintaining and improving the safety, wholesomeness, and nutritional quality of the national food supply. Through scientific research, consumption surveys, compliance programs, and assistance to local, State, and international groups, CFSAN encourages the prevention of food-borne injury and disease.

The Center for Veterinary Medicine is responsible for evaluating the safety and effectiveness of animal drugs and animal-feed additives and for setting tolerances for residues of these substances in food-producing animals. The demonstration of safety is based on the use of risk assessment and risk management.

The Center for Devices and Radiological Health develops and carries out a national program designed to control unnecessary exposures of humans to, and assure the safe and efficacious use of, ionizing and nonionizing radiation-emitting electronic products. It also develops and carries out a national program to assure the safety, effectiveness, and labeling of medical devices for human use. It plans, conducts, and supports research and testing to provide the scientific and technological base required for risk assessment, evaluation, compliance, and performance standards development relating to medical devices and radiation-emitting electronic products.

FDA's assessment of drugs and biologics takes place in the Center for Drugs and Biologics. Biologics are products having a biological origin and include blood products and vaccines used in the prevention, treatment, and biologic cure of diseases or injuries in humans. Drugs and biologics for human use have particular considerations in risk assessment because of their importance and widespread use and because assessment of their benefit must be done in concert with an assessment of their risk.

The National Center for Toxicological Research (NCTR) was established to address the uncertainties caused by assumptions used in risk assessment and to develop risk-reduction strategies. It is a "common ground" where scientists throughout government and in all sectors of society can address problems of mutual interest germane to these tasks. Although some of the Center's resources are used to generate data for hazard identification and dose-response assessment (almost all as a contribution to NTP), most resources are devoted to research for solving problems in risk assessment and risk reduction (for example, biomarkers, elucidation of the factors that modulate toxicity in vivo, and testing the assumptions underlying risk assessment).

Office of the Assistant Secretary of Health (OASH)—OASH performs a variety of activities in risk assessment and risk management. It administers the largest hazard-identification program in government, provides statistical data for aspects of risk assessment, performs risk assessments for other parts of DHHS and for its own programs, and manages risk by public dissemination of health-related information.

The National Center for Health Statistics (NCHS) provides information on exposure assessment, hazard identification, and risk characterizations from population surveys and a variety of record systems. In addition, the NCHS staff participates in planning studies associated with risk assessment through the National Death Index, provides technical assistance to persons planning health-examination studies, and provides biologic samples or data from various NCHS activities. Some periodic studies involve direct risk assessment, such as the National Health and Nutrition Examination Surveys (NHANES).

The National Center for Health Services Research (NCHSR), through Public Law 89-97 (the Medicare Law), determines, via its Office of Health Technology Assessment, the safety and efficacy of treatments to be used in Medicare patients. It supplies these risk assessments and recommendations to the Health Care Financing Administration (DHHS), which evaluates them as a basis for action.

The National Toxicology Program (NTP) brings together significant toxicology research and testing activities of the relevant DHHS research agencies to develop (and provide) needed information to regulatory as well as research agencies and to strengthen the science base. The NTP's predominant long-term objective is the development, validation, and application of better, less expensive, and more specific test methodologies. However, studying chemicals for toxicologic endpoints continues to be a central focus and utilizes the most resources. By broadening the protocols to better characterize the chemical toxicologic profile, the NTP has implemented a comprehensive approach to assessing chemical toxicity which includes carcinogenicity, genetic toxicity, teratogenicity and other reproductive effects, chemical disposition, and general toxicology. Resources for the NTP originate from NIEHS, NCTR, NIOSH, and ATSDR.

The Executive Committee, Committee to Coordinate Environmental and Related Programs (CCERP), serves as the primary entity in DHHS for the formulation, monitoring, and implementation of environmental health policy. It makes its recommendations to the Secretary through the Assistant Secretary for Health.

CCERP was established by the Assistant Secretary of Health to: 1) provide a medium to assure the exchange of information on environmental health, toxicology, and related programs; 2) coordinate these programs; 3) enhance the sharing of resources; and 4) provide advice to the Department. In January 1984, the Assistant Secretary for Health chartered a Standing Subcommittee for Ad Hoc Chemical Risk Assessments to: 1) develop processes and procedures to assure rapid coordinated development or review of ad hoc risk assessments; 2) enhance communications and information flow among various agencies concerned with risk assessments; and 3) recommend to the Executive Committee, CCERP alterations in these procedures and processes as warranted, given changes in the state-of-the-science or expertise.

The Office on Smoking and Health (OSH) compiles the annual report on the health consequences of smoking, required by Public Law 91-222 (the Public Health Cigarette Smoking Act of 1969) and its predecessor, the Federal Cigarette Labeling and Advertising Act. The Office assesses the various health risks of smoking and conducts campaigns to encourage the public to stop smoking. The activities of OSH are supported through many agencies of the PHS.

4.4 PROBLEMS IN RISK MANAGEMENT

Over the years, many acts, regulations, and executive orders have been promulgated to control the release and dissemination of hazardous agents into the ambient and workplace environments; to control hazards in food, drugs, and commodities; and to regulate risk-reduction strategies. These acts reflect the scientific and societal viewpoints that existed at the time of their enactment. As a result of the diversity of statutes and responsibilities of the different units in DHHS—in part a vestige of the way in which DHHS was formed—the conception of health risks and the view on how to manage risks posed by chemicals with toxic effects may vary among the agencies. Thus, more than one agency under more than one act may regulate the same substance, one act may involve more than one agency, and several acts may address risks to specific subgroups of the population. For example, legislation on the hazard posed by exposure to lead is covered, among others, by the Occupational Safety and Health Act (involving NIOSH); the Safe Drinking Water Act (involving CEH); the Comprehensive Environmental Response, Compensation, and Liability Act (involving ATSDR and CEH); the Resource Conservation and Recovery Act (again involving ATSDR and CEH); and the Public Health Service Act (involving the NIH, FDA, and CDC). In addition, some of these acts involve other departments and independent agencies (for example, the Safe Drinking Water Act involves the Environmental Protection Agency (EPA); the Occupational Safety and Health Act involves the Department of Labor; the Lead-Based Paint Poison Prevention Act involves the Department of Housing and Urban Development, the Consumer Product Safety Commission (CPSC) as well as DHHS; and the Consumer Product Safety Act directly involves CPSC).

The diversity of acts and agency approaches may have some advantages, but it also increases the likelihood of problems of consistency, integration, and general applicability. The complexity of the management of toxic substances is also increased by the involvement of nonregulatory agencies in risk management through interagency agreements or their respective missions.

In addition, risk managers are faced with differences in the public perception of risk when setting standards for maximum exposure levels and developing or advising protective measures and other remedial activities (see Section 6). These differences become apparent when, in public meetings, such questions as the following are asked: a) what level of risk distinguishes acceptable from unacceptable risk; b) should the same threshold be established for food products as for drinking water or ambient air; c) should a toxic substance with certain recognized benefits be controlled rather than banned; and d) to what extent should cost factors be considered in the design and implementation of proper and adequate risk management?

The need to control the risks from toxic chemicals and the need to deal with the differences in the public's perception of risk are major considerations in the management of risks by the government. In DHHS, risk management has two kinds of facets: regulatory and nonregulatory. Nonregulatory facets include such wide-ranging activities as public education, providing advice to other Federal and State departments, disseminating information, evaluating risk management in specific hazardous situations, and helping to prepare and evaluate regulatory risk management. The diversity among DHHS units in their involvement with and their approaches to risk management may pose problems for the Department in developing and conducting consistent, rational, and societally acceptable risk management. Sections 8 and 9 illustrate these problems and an approach for resolving them.

SECTION 5: RESPONSES OF DHHS AGENCIES TO SURVEY QUESTIONNAIRE

5.1 INTRODUCTION

Section 4 provided an overview of the PHS agencies that conduct risk assessments and/or have risk-management responsibilities. Information bearing on specific activities in this regard was sought by use of a survey questionnaire directed to organizational units in the PHS agencies (questionnaire is Subsection 12.2 in the Appendix). This section gives an overview of some of the points gained from the survey questionnaire. It must be reemphasized that time constraints precluded the opportunity for pretesting the questionnaire, and, consequently, variability in interpreting the questions resulted in data that could be misleading. For these reasons, the following comments are general and are restricted to Part 4 of the questionnaire.

The units were asked to provide the following information:

- Definitions of terms used in the processes of risk assessment and risk management.
- Mission statement and legislative mandate.
- Philosophy of risk used by the agency.
- Procedures used in the conduct of risk assessments and risk-management actions.
- Resources devoted to research applied to risk assessment and risk management and which generates data for these processes.
- Research recommended for enhancing risk assessment and risk management.

5.2 PHS AGENCIES SURVEYED

Organizational units of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and, in addition, the Office of the Assistant Secretary for Health (OASH), DHHS, were surveyed. Replies were received from 26 of the organizational units within these entities.

5.3 PART 4 OF QUESTIONNAIRE — GENERAL INFORMATION

Part 4 of the survey questionnaire sought general information on the extent of specific agency involvement in risk-assessment and risk-management actions and inquired about procedures involving these two processes. Some general observations are:

- Each PHS agency and OASH reported involvement in risk-assessment activities to some extent. This included a total of 13 separate organizational units within these five agencies.
- All agencies are involved in aspects of risk-management activities.
- Of the organizational units reporting risk-assessment involvement, three stated that they had a written agency policy for the conduct of risk assessment.
- Of the organizational units reporting risk-assessment activities, most stated that they conduct some form of scientific peer review and/or public review of risk assessment.
- Eleven of the organizational units reporting risk-assessment activities reported interaction with other Federal agencies or State/local governments. The number of organizations reporting coordination with other Federal agencies was about twice the number reporting coordination with State/-local governments.
- More units are involved in qualitative rather than quantitative risk assessment activities—with the preponderance of the risk assessments being qualitative rather than quantitative.

SECTION 6: A PHILOSOPHY OF RISK

6.1 INTRODUCTION

The question of what should constitute a philosophy of risk is a difficult one. In answering this question, the definition of philosophy was selected from several possible definitions (8). This Report defines philosophy as "a set of motivating concepts or principles." Several concepts or principles were important in shaping the philosophy of risk given in Subsection 6.8. Six select concepts that contribute to formulating a philosophy of risk from toxic substances are discussed briefly in Subsections 6.2-6.7.

6.2 STATUTORY CONCERNS

In Subsection 4.2.2, it is noted that the public expects the government to act to manage risks associated with toxic effects. At the national level, this expectation led Congress to enact laws to control risks to public health that authorize various Federal agencies to identify and control risks. Several State, and some local, governments have enacted similar laws. One consequence of this legislative approach to risk management is that the authorized Federal agencies must act within the limits imposed by the authorizing legislation. In some instances, the statutory language is precise, and DHHS actions are prescribed in the statute. For example, the Delaney Amendment requires the Food and Drug Administration to ban food additives that are carcinogens in humans or animals. Other statutes, such as the Occupational Safety and Health Act, authorize the Department to identify health risks, but the method of controlling the risks is not prescribed. Thus, the Department's role in risk management is constrained by legislation enacted by Congress. Any DHHS philosophy of risk must be compatible with applicable legislation.

6.3 ACCEPTABILITY OF RISK

Some risk is inevitable in life; this concept is not new or unusual. Our ancestors had to contend with the risks to health posed by infectious diseases, poor sanitation, and adulterated food. Each of these risks has been markedly reduced in the United States, mainly in the 20th century. However, because of changes in such elements as industrial technology, socioeconomic factors, and lifestyle, other risks have been identified. The kinds and degrees of risk that we are exposed to, and are willing to accept, have also changed. For example, now that vaccines and immunization programs are available to prevent many once-common diseases, the public is not readily willing to risk outbreaks from infectious agents, especially since outbreaks appear to be readily avoidable through a fairly simple control procedure. Instead, the degree of risk posed by noninfectious disease and toxic substances is now a major concern. Also, as individuals, we seek a reasonable assurance that the environment surrounding us and the products we use will not cause adverse human health effects. On the other hand, the public may prefer to tolerate some avoidable risks compared to their practical alternatives. For instance, the carcinogenic risk of certain chemotherapeutic drugs is weighed against the risk of death from not treating the cancer. This concept of relative risk is especially important in risk management of drugs, but may be relevant for risk management of other substances (for instance, the risk of allowing contaminated mud to lie on a lake bottom versus the risks associated with dredging the mud). Two very different activities are, therefore, part of a risk-management decision: 1) measuring risk, an objective but probabilistic pursuit (as discussed in Section 7); and 2) judging the acceptability of that risk; a matter of judgment including scientific, legal, moral, and societal values. Acceptability, or willingness to tolerate risk, is not a fixed quantity. What was acceptable in the past may not be acceptable today. As exposures alter, as mores change, as prevention and control techniques improve, as the laws evolve, as needs arise, as information on health hazards increases, as alternatives become available, acceptabilty changes. For DHHS, legal considerations are very important in judging acceptability, however, the other factors listed above, working both on the law and the procedures that each agency has adopted to protect the public health, influence what risks are and are not acceptable at any point in time. Also, it should be realized that public acceptibility may be different from acceptibility to the units in DHHS, which should be taken into account when the risk is being discussed.

6.4 ESTIMATION OF RISK

The nature and precision of the data available, and the intended use of risk information, are important determinants of the public's perception of the nature of risk. How well the numerical value of risk can be specified is largely dependent on the availability of relevant data. Actuarial studies of overall life span in large populations can specify, with considerable accuracy, the risk of death from any cause, given a few basic characteristics of the individual, such as age and sex. At the other extreme, the estimation of the risk of an event that has never occurred, such as the risk of "meltdown" in a nuclear power plant, is entirely theoretical and is made through the synthesis of risk estimates of the various steps in a hypothetical scenario leading up to the final event. In the case of many human health effects related to chemical toxicants, the data lie somewhere between the two extremes of the actuarial and the theoretical. Data are placed into a useful context by the use of inferences, which are based on assumptions. These assumptions may have differing degrees of validity, thus leading to uncertainty in the inferences, although the data used may be accurate. This uncertainty can influence public perception of risk.

Another determinant is the intended use for the data. Use of risk information falls principally into two categories. Economists, planners, and government agencies use risk information to make operational decisions about other activities that cannot be optimized without knowledge of risks (for example, the determination of premiums that should be charged for insurance). Health workers are chiefly concerned with developing or exercising options for the reduction of demonstrable risks that are susceptible to intervention. For either purpose, risk may at times be attributable to an individual, using a relatively large number of characteristics, such as personal medical history, weight, habits, etc., or to a population, group, or a business, using few characteristics. When a physician recommends that a middle-aged patient without immediate evidence of chronic disease lose weight, stop smoking, etc., the physician is intuitively synthesizing risk information derived from previous clinical research with his or her perceptions of the characteristics of the given individual that bear on risk estimates and advising modification of lifestyle for the purpose of reducing that risk. This can be termed personal risk, and most people are acquainted with and understand this type of risk. Many people transpose risks of all types to this immediate and personal type. Risks of toxic effects from substances are inferential by nature and are almost always applied to a population or an idealized "average" person.

6.5 VOLUNTARY ASPECTS OF RISK

Another important concept in developing a philosophy of risk is the voluntary nature of risk. People knowingly assume some risks, while other risks are imposed by conditions over which they have little or no control. In a pragmatic sense, one may be able to distinguish between voluntary risks (those a person assumes by voluntary action) and involuntary risks. In the context of toxic substances, a voluntary risk would be one assumed by a person who used exposure to psoralen and ultraviolet light to treat psoriasis, while being fully aware of the risk of cancer formation associated with that treatment. An example of an involuntary risk would be one posed by an unrecognized chemical carcinogen in a community's food or drinking water. Sometimes, depending on the context, the distinction between voluntary and involuntary risks is unclear. For example, is the risk voluntary or involuntary when a person knowingly drinks polluted water because no other water is available? The voluntary nature is important in the perception of risk. In general, the public is less tolerant of involuntary risks, as shown by the legislation to control unwanted environmental risks from toxic substances.

6.6 PERCEPTION OF RISK

People respond to the hazards they perceive. The effectiveness of risk-management efforts depends, in large part, on the public perception of risk. Several psychologists have studied the process by which people judge risk and how lay people and safety experts perceive risk (8-10). They concluded (8):

- Cognitive limitations, coupled with the anxieties generated by facing life as a gamble, cause uncertainty to be denied, risks to be distorted, and statements of fact to be believed with unwarranted confidence.

- Perceived risk is influenced (and sometimes biased) by the imaginability and memorability of the hazard. People may not, therefore, have valid perceptions even for familiar risks.
- The safety experts surveyed evidenced perceptions of risk that closely corresponded to statistical frequencies of death.
- Lay persons' risk perceptions were based only in part on statistical frequencies of death. Their risk perceptions also included qualitative aspects such as dread, the likelihood of a fatality, and the degree of catastrophic potential. Lay people also rated involuntary risks as being more threatening than voluntary ones.

Thus, the public's perception of risk may differ from that of trained experts. Government personnel must understand and act on these different perceptions in the course of risk management. For example, the risk management of a toxic dump site should take into account the public's perception of the hazards. If reports of hazards from waste dumps have recently appeared in the news media, they will color the public's imagination and noteworthiness of problems associated with any waste dump in their locale. Risk managers would need to factor this perception of the public into their risk-management actions (that is, they may need to educate the public rather than ban the substance).

6.7 THE PROCESSES OF RISK ASSESSMENT AND RISK MANAGEMENT

The processes by which risks are identified, evaluated, and managed are described in Sections 7 and 8, but brief comments are appropriate here (11, 12). Both the government and the public should recognize and understand that risk-assessment and risk-management analyses are probabilistic and uncertainites are associated with them; that the science of risk assessment will improve with time as scientific knowledge increases; that risk management will improve through experience; and that as risks are reduced, any additional costs (social and economic) should be communicated to the public. The central concept is the importance of educating the public about the nature of risk assessment and management.

6.8 DHHS STATEMENT OF A PHILOSOPHY OF RISK

Information in this Report leads to a statement of a philosophy of risk that DHHS may be able to adopt as a generic concept. This philosophy could be amended by individual agencies where appropriate and necessary, for example, when statutory language dictates an agency-specific philosophy of risk.

Philosophy of risk—Individuals have always lived with risk, presently live with risk, and will continue to live with risk in the future. Some degree of risk of adverse health effects from toxic substances is inevitable, as a consequence of exposure to both naturally occurring and manmade toxicants. The public should be made aware of the nature of the risk. Public health risks that are not acceptable should be reduced or eliminated when feasible. Means to accomplish this goal should not pose additional significant risks.

The following actions should be considered in putting this philosophy into practice:

a) Identify hazards that pose risks to public health and well-being.
b) Manage risks associated with the identified hazards in a manner that is prudent and in concert with the public's need.
c) Acknowledge the essential participation of the public.
d) Communicate risks understandably to both experts and lay persons.
e) Whenever possible, use information that makes it possible to arrive at an informed estimate of risk.
f) Manage each significant risk through an approach that gives full consideration to alternative actions to control the hazard.
g) Advance the processes of risk assessment and risk management by research that reduces uncertainties.

SECTION 7: THE ASSESSMENT OF RISK

7.1 DESCRIPTION OF THE PROCESS AND ITS RELATED UNCERTAINTIES

The process of risk assessment, a process that is still very much in transition or evolution, is often a mixture of scientific facts, consensus, assumptions, and science policy decisions (i.e., policy statements made by agencies to resolve points of current controversy). It is typically depicted in terms of four steps: hazard identification, exposure assessment, dose-response assessment, and risk characterization. However, all four of these steps are not necessarily involved in any given situation requiring risk assessment. For example, many risk assessments conducted within DHHS may rely on hazard identification alone or primarily on hazard identification and exposure assessment, with less emphasis on risk quantification, particularly as developed through mathematical modeling.

In this section, the four steps are discussed in some detail, the strengths and limitations of the data involved in each step are considered, the primary assumptions most commonly employed in the process are identified, and current approaches for dealing with the uncertainties in the process are briefly reviewed. Potential risks or endpoints of interest in the assessment process can range from sensory irritations, reversible physiologic changes, and acute traumatic injury to irreversible organ-system damage, adverse reproductive outcomes, major genetic alterations and mutations, chronic diseases, such as cancer, and death. Much of the risk-assessment methodology development, however, has occurred primarily in the areas of carcinogenesis and, to a lesser extent, mutagenesis and teratogenesis.

7.1.1 Hazard Identification

Hazard identification is largely a judgmental process that requires the expert knowledge and experience of scientists from a variety of disciplines in interpreting the best available information. During this phase of the risk-assessment process, a question that may be asked is whether the agent under consideration has the potential to produce adverse health effects. This is one approach. Another approach addresses an adverse health outcome to see if it might have been caused by a chemical agent. Some important historical examples concerning this latter approach are noteworthy in that, in most cases, the discovery was precedent-setting; that is, the agent responsible for the disease was from a class of substances not previously under suspicion. The classic example is Percivall Pott's description, in 1775, of cancer of the scrotum in chimney sweeps, which is acknowledged as the first recognition of a chemical as a carcinogen. Pott's observation left no doubt this was a recognized occupational cancer in youngsters. Other examples include: lung cancer traced to either cigarette smoke or asbestos dust, angiosarcoma of the liver traced to vinyl chloride, adenocarcinoma of the vagina in women whose mothers were given DES, and phocomelia (shortened limbs) traced to thalidomide.

Hazard identification relies primarily on results generated from clinical and epidemiologic studies and from animal toxicologic experiments. Other types of information that may, when available, contribute to the hazard identification process include: short-term in-vivo and in-vitro test results; comparative metabolism and kinetic information; and available data on the physiologic, pharmacologic, biochemical, chemical, and physical properties of the chemical of interest. Much of the data included in these latter categories relates to the issue of mechanisms of action and is receiving increasing attention in hazard identification.

The primary advantage of epidemiologic data is that such data permit the direct evaluation of potential health risks in humans. This avoids the problem of species extrapolation and its attendant uncertainties. The reliability of epidemiologic data in hazard identification is increased when the results:

- Are derived from well-designed and well-executed case-control or cohort studies that are free of bias;
- Display a strong association unlikely to be due to chance variation;
- Follow a logical, temporal sequence of exposure-response;
- Have been replicated in a variety of settings;
- Exhibit a dose-response relationship;
- Are toxicologically plausible.

Epidemiologic studies with negative outcomes can also provide an indication (through the use of upper confidence limits) of the likelihood of health risks associated with the chemical exposure under investigation.

Although the epidemiologic approach is focused directly on human experience, a number of limitations can affect its usefulness in hazard identification:

- In prospective follow-up studies involving chronic diseases with long latency periods, not enough time may have elapsed since the initiation of exposure for there to be sufficient (or even any) response data from the study population. Acquisition of such data could be extremely time-consuming and expensive.
- When epidemiologic data are generated retrospectively, follow-up of the study population may be relatively complete, but the quality of the corresponding historical exposure data may be inadequate. (Lack of adequate exposure data may be a significant, limiting factor to the usefulness of epidemiologically derived results.)
- Because sample size is frequently dictated by cost considerations or the availability of subjects, studies may lack sensitivity (power) to detect health effects of low or even moderate magnitude.
- Case-control studies, which can complement cohort studies and which are an important epidemiologic approach to identifying potential human health hazards, can be affected by recall bias, control selection, and other confounding variables associated with this methodology.
- Results may be confounded by the presence of other exposures or risk factors that are beyond the investigator's control and not amenable to statistical adjustment.

As part of the effort to limit some of the problems that can be encountered with this approach, increasing emphasis is being placed on the incorporation of biochemical and molecular laboratory methods in analytical investigation.

Clinical reports are another source of useful information in identifying hazards. These reports typically describe the health effects of a hazard in persons who require clinical intervention. Often, the clinical report presents new information on a hazard not previously identified, and epidemiologic studies of a follow-up or cohort nature are stimulated to clarify the health risks. The principal limitations of clinical reports for the process of hazard identification lie in the potential uncertainties about the patients' exposure to the alleged hazard, the possibility that chance variation or selection factors may account for a "cluster" of cases traced to a particular exposure, the inability to identify hazards that result in clinical effects after long latent periods, and the low probability of recognizing an effect that is merely an increase in the risk of an event with a high background rate.

Results from animal toxicologic studies are used to identify potential hazards to humans and to complement or supplement the findings from epidemiologic investigations. In the absence of relevant epidemiologic data, these animal studies serve as the primary data base in human health hazard identification. For example, the International Agency for Research on Cancer (IARC) has stated that "in the absence of adequate data on humans, it is reasonable, for practical purposes, to regard such chemicals (that is, chemicals for which there is 'significant' evidence of carcinogenicity in animals) as if they presented a carcinogenic risk to humans."

The reliability of results derived from animal experimentation is increased if:

- They can be replicated in more than one experimental setting, species, strain, and/or (when appropriate) sex.
- They exhibit a dose-response relationship.
- They are based on a dosing regimen and route of exposure similar to that likely to be encountered by humans.
- The test animal employed in the experiment is known to, or is likely to, process (i.e., absorb, metabolize, excrete, etc.) the test chemical in the same or similar manner as humans.

As with epidemiologic investigations, animal laboratory studies have certain limitations:

- Such studies can take a long time to conduct and can be costly.
- Because of practical constraints on sample sizes, animal studies may lack sensitivity and may detect only pronounced health effects.(Incorporating high doses into the experimental design to enhance the likelihood of observing a response may introduce additional problems in some instances.)
- As a result of species and strain variability in sensitivity, the test model or models selected may be overly resistant or susceptible to the toxicologic effects of the agent studied.

When health-hazard identification is based largely or exclusively on laboratory-generated data, consideration should be given to known species factors and to exposure conditions that could contribute to differences in the response between test animals and humans.

Finally, all relevant data should be considered in the process of hazard identification. Some hierarchical structure may be imposed on the data to aid in the evaluation—for example, a structure based on varying degrees of experimental evidence such as the IARC and NTP classification schemes for carcinogens. Assuming adequate experimental design, both positive and negative results should be considered. Then, the greater the consistency of the data, the stronger the inference that can be drawn about the presence or absence of a potential human health risk.

7.1.2 Exposure assessment

Exposure assessment deals primarily with estimating the types, magnitudes, and durations of actual or anticipated exposures to hazardous agents. When appropriate, determining the size and composition (age, race, sex, etc.) of the exposed population may also be considered. Exposure evaluation is an extremely important component of the risk-assessment process, particularly with regard to the quantification of potential human health risk. The lack of adequate exposure data may significantly lessen the value of any epidemiologic information.

Exposure assessment is typically based on monitoring studies that involve direct measurement of exposures, mathematical modeling, and the study of microcosms or mini-environments, or some combination of these approaches. Monitoring studies can focus on the individual (for example, history of medication use, dietary profiles, and screening studies for biochemical markers); the home (for example, indoor air pollution resulting from formaldehyde insulation, combustion products from heating appliances, radon daughter products from building materials, and cigarette smoke); the workplace (which may be complicated by difficulty in separating or identifying individual components of a complex mixture or manufacturing process); or the ambient environment. In addition to being directly applicable in a given assessment, data from monitoring studies may also be used to help develop mathematical models for predicting future anticipated exposure levels. Mathematical models are most useful for generating average or "expected" levels of exposure, but can be misleading when they oversimplify the actual exposure phenomenon or are applied to inadequate or inappropriate data. Finally, microcosms attempt to create a mini-environment in the laboratory and, in the absence of adequate data on transport and transformation processes, can serve as an alternative to mathematical models.

A number of factors make exposure assessment one of the more difficult components to conduct adequately in risk assessment. When exposure involves concurrent exposure to a number of different chemicals, there may be potential for additive, synergistic, or antagonistic effects that are often ignored. The problem is even more difficult when exposure occurs as a complex mixture of chemicals. In such instances, one may not even be able to identify the chemical, or combination of chemicals, most likely to pose a threat to human health, and so exposure quantification becomes extremely complicated, if not impossible. Exposure often varies widely within a population, and even for a given individual, and may not be adequately characterized by a single value such as the average exposure level. For example, peak or maximum exposures may be more important than average exposures in determining potential health risks. The duration of exposure is another difficulty in the estimation of risk in situations of less-than-lifetime exposure. Questions about trace levels of exposure and the bioavailability of a given chemical may be difficult to address quantitatively in environmental risk assessments. Exposure assessments typically focus on the "external" or "observed" exposure level rather than the "biologically effective" dose, which may not be proportional to the observed dose. Finally, a relationship may exist between a given health outcome and the timing of exposure, such as initiators or promoters in carcinogenesis, or the critical developmental period in teratology.

All potential sources and routes of exposure to a specific chemical should be taken into account, with the relative significance of each individual source as well as the magnitude of the overall exposure being indicated when possible.

7.1.3 Dose-response assessment

Dose-response assessment is concerned with the evaluation and quantitative characterization of the relationship or association between the level of exposure to the agent under study and the toxicologic response or responses that are elicited by such exposure, particularly as it applies to humans. The techniques most frequently used in this quantification process are the safety-factor approach, margin-of-safety procedure, and mathematical modeling.

Safety factor—The safety-factor approach may be the most commonly employed procedure for estimating risk when the endpoints are noncarcinogenic. It is used to determine an "acceptable" or "allowable" human intake level of a toxic agent. Specifically, a no-observed-effect level (NOEL) or, in some instances, a lowest-observed-effect level (LOEL), for the agent is estimated epidemiologically, clinically, or through chronic animal toxicity testing and then divided by an "appropriately chosen" safety factor that reflects such considerations as the type of toxicologic outcome under study and the quality of the available data. The safety-factor approach has been widely used because it is simple to apply and understand. On the other hand, a number of potential problems are associated with it, such as:

- Dependence on the particular experimental conditions:
  - —Sensitivity of the test species or strain utilized.
  - —Sample sizes employed.
  - —Number and spacing of experimental dose levels.
- Failure to take into account the shape or slope of the dose-response curve.
- Implication of the existence of an actual or practical threshold, a condition that may be difficult to justify biologically and to estimate empirically.

Margin of safety—The margin-of-safety procedure is closely related to the safety-factor approach. In this case, the estimated NOEL, or LOEL, often based on human data or, in their absence, the most sensitive species tested, is divided by the estimated human exposure level, and the resulting "margin of safety" is evaluated for its adequacy. The magnitude of this ratio (the margin) provides some idea as to the proximity of an exposure level to one that may cause adverse health effects. This procedure allows flexibility in regulating exposure, since it is does not state a defined safety level. It is widely used in occupational health. Because of its similarity to the safety-factor approach, it has many of the same problems associated with its use and the additional uncertainty involved with estimating the human exposure level.

Mathematical modeling—Mathematical modeling is usually employed in toxicologic risk estimation to depict the underlying dose-response relationship for the purpose of generating estimates of and upper bounds on the unknown low-dose risk. It is also used to develop estimates of potency that do not necessarily involve low-dose extrapolation. Model development has been particularly prominent for carcinogenesis, although mutagenesis and teratogenesis have also received some attention. As was the case with the safety-factor approach, a number of problems can be encountered when mathematical models are used. Mathematical models typically oversimplify the underlying biologic mechanisms that they attempt to depict. In addition, they are often based on assumptions that are not readily experimentally verifiable. Furthermore, when applied naively, or when inadequately qualified, they may imply a greater sense of scientific precision than is actually warranted.

When experimental data form the basis of dose-response assessment, several factors can contribute to differential responses between experimental systems and humans and, therefore, can complicate the extrapolation of observed effects across species. These factors include interspecies differences in lifespan; body size; genetic variability within the population; concurrent disease; and pharmacokinetic factors such as absorption, metabolism, excretion, and exposure regimen (i.e., route, dosing schedule, duration of exposure). Although these factors should be considered when toxicologic effects are extrapolated across species, in many instances appropriate data, particularly information on mechanisms of action, effective target dose, etc., will not be available. As a result, a more empirical approach to species scale-up is usually employed. Specifically, it is often assumed that toxicologic responses will be "equivalent" across species when expressed in terms of an "appropriately chosen" common dosage scale.

7.1.3.1 Carcinogenesis

Several different quantitative models have been proposed for low-dose extrapolation in carcinogenesis. These models are often categorized as tolerance distribution models, mechanistic ("hit") models, or time-to-tumor models. The tolerance distribution models assume that each individual in the population has a tolerance level below which he or she will not respond and that the variation in individual tolerance levels can be described by some statistical distribution. The mechanistic models are based on the assumption that cancer originates in a single cell that undergoes a series of somatic mutations. Finally, the time-to-tumor models attempt to characterize the complex relationship between tumor latency, dose, and the risk of cancer. In addition to these classes of models, a linear model or some adaption of it is often used to place an estimated upper bound on that portion of the underlying dose-response function that is assumed to be convex in the low-dose region. Although the multistage model or one of its variants is the most commonly employed of the current extrapolation models, no single model is recognized as being the most appropriate for low-dose carcinogenic risk estimation. The choice of a particular model for estimating effects at low doses can be a critical element in the risk-assessment process. Depending on the given data set and the extent to which extrapolation is carried out beyond the observed data range, low-dose risk estimates derived from different models may be in relatively close agreement or they may differ substantially. A discussion of the various models that make up the above categories and of their relative strengths and weaknesses can be found in a number of standard references, such as Chapter 6 of the OSTP document (2).

In addition to the selection of a particular extrapolation model, a variety of other factors can also significantly affect low-dose risk estimation, such as:

- The possibility of synergism or antagonism associated with the multiple exposures typically encountered in the human environment.
- The manner in which background incidence rates are incorporated into the model, that is, whether they are treated as an independent or additive process. (If only a small portion of the background is assumed to be additive, then the model will be mathematically linear in the low-dose region, and marked discrepancies between different model estimates are unlikely to occur.)
- The availability of information on pharmacokinetics, mechanism of action, effective target dose, etc. (for example, if the relationship between administered dose and effective target dose is nonlinear, incorporation of pharmacokinetics into the modeling process can significantly modify low-dose risk estimation, regardless of the model employed).
- The way in which incomplete or short-term exposure and follow-up are addressed when dealing with epidemiologic data.
- The empirical approach to species extrapolation in carcinogenesis has tended to rely on the use of a milligram per kilogram (mg/kg) bodyweight per day (that is, based on body size), parts per million (ppm) in the diet (based on concentration), milligrams per square meter of surface area per day (that is, based on body surface area), or mg/kg in a lifetime (based on size and species longevity) dosage scale. Low-dose risk estimates can vary by as much as 40-fold, depending on the choice of a particular dosage scale. No single scale has been consistently employed or agreed upon by scientists in the field.

7.1.3.2 Mutagenesis

Less attention has been given to mathematical modeling in mutagenesis than in carcinogenesis. However, the NAS Committee on Chemical (Environmental) Mutagens (13) concluded: "Unless there is evidence to the contrary, it will be assumed that there is no threshold. If it is necessary to extrapolate from high-dose data, the best procedure is to interpolate linearly between the effect at zero dose and the lowest reliable data point(s)."

In mutagenesis, as in carcinogenesis, risk-assessment research has emphasized the development of standardized dosage scales or baselines for quantitative extrapolation of mutational events across species and of biochemical methods for determining the genetically effective dose in the target tissues. Although several different dosage scales have been explored, none has yet gained recognition as the most appropriate for species extrapolation.

Finally, it is important to note that mutagenic risk assessment is further complicated by the fact that even if one can generate an estimate of the potential increase in the human mutation rate resulting from exposure to some hazardous agent, the probable impact of this increase on human health must still be ascertained.

7.1.3.3 Teratogenesis

Teratogenesis is also a difficult area of toxicology to address from the point of view of risk assessment, since the target organism is actually the entire maternal-placental-conceptus complex and since little is known about the underlying biologic mechanisms. Additional issues that need to be considered when undertaking dose-response modeling or species extrapolation in this area include:

- Litter effects, that is, the tendency for fetuses from the same litter to respond more alike than fetuses from different litters.
- Potential association between developmental alterations and maternal toxicity.
- Possibility of threshold effects.
- Interspecies differences in the timing of developmental events.

Although risk assessment in teratogenesis has relied primarily on the safety-factor approach, research into dose-response modeling, species extrapolation, and other related issues is being encouraged and pursued.

7.1.4 Risk characterization

Risk characterization, the final step in the risk-assessment process, involves a multidisciplinary evaluation of all relevant data on hazard identification, exposure assessment, dose-response, and species extrapolation to reach an overall determination of the health risk posed by anticipated or known exposures to a given agent. Because of differences in human susceptibility and exposure conditions, some consideration should be given, when possible, to the identification of high-risk subgroups in the general population at this phase of the process.

For the decision maker to have a more complete appreciation of the strengths and limitations of the process as applied to the agent of interest, the various sources of uncertainty in the assessment should be described and, if possible, quantified. In addition, a distinction among facts, consensus, assumptions, and science-policy decisions in the risk-assessment process should be made and communicated to those involved in risk management.

7.2 COMMON ASSUMPTIONS IN RISK ASSESSMENT

As indicated in the preceding subsection, assumptions frequently need to be made at each phase of the risk-assessment process to fill in various gaps in the underlying scientific data base so that the assessment can be completed. For example, the NAS report on risk assessment (1) identified several instances in the "typical" risk assessment when scientific inferences (assumptions) might have to be made because scientific knowledge or specific information about the hazardous agent under evaluation is missing. The NAS report also noted that this list of inference options was incomplete, that not all options would be used in every risk analysis, and that the impact of different options could be quite variable. Thus, any thorough enumeration of the assumptions underlying the risk assessment process and an evaluation of their significance must be approached on a case-by-case basis. Several common assumptions seem to be made in many risk assessments—assumptions that are generally regarded as affecting the final assessment of risk. However, many of these assumptions are consensual and require further validation. Among these assumptions are the following:

- In the absence of adequate human data, adverse effects in experimental animals are regarded as indicative of adverse effects in humans.
- Dose-response models can be extrapolated outside the range of experimental observations to yield estimates or estimated upper bounds on "low-dose" risk.
- Observed experimental results can be extrapolated across species by use of an appropriately chosen standardized dosage scale.
- No threshold for carcinogenesis exists, although threshold effects may apply for other toxicologic outcomes.
- Average doses give a reasonable measure of exposure when dose rates are not constant in time.
- In the absence of pharmacokinetic data, the effective or target dose is assumed to be proportional to the administered dose.
- The risks from multiple exposures and multiple sources of exposure, to the same chemical, are usually assumed to be additive.
- Regardless of the route of exposure, 100% absorption across species is assumed in the absence of specific evidence to the contrary.
- Results associated with a specific route of exposure are potentially relevant for other routes of exposure.

In any given risk assessment an attempt should be made to identify clearly all major assumptions that have been made and to indicate, if possible, their probable effect on the risk-assessment process.

7.3 DEALING WITH UNCERTAINTIES IN THE PROCESS

As indicated in the introduction to this section, risk assessment is not a static process but is clearly in transition or evolution. This evolutionary nature is, perhaps, best characterized by the increasing emphasis that is being placed on identifying and reducing the uncertainties associated with the process.

To reduce the uncertainty associated with the lack of reliable data, various organizational units in the Department are attempting to improve or expand current data bases on human exposures and responses, or health effects, and to characterize more fully the toxicologic profile of various hazardous agents from an experimental viewpoint.

Similarly, a number of units in the Department are also conducting basic and applied research in toxicology, biochemistry, oncology, statistics, epidemiology, biomathematics, and other fields, which has borne, and will continue to bear, on some of the uncertainties in the risk-assessment process posed by the lack of both general and specific scientific knowledge.

In addition to the focus on reducing uncertainty in the risk-assessment process, there is also a growing recognition of the importance of clearly qualifying and, when possible, quantifying uncertainties associated with risk-assessment activities as they are currently practiced. The OSTP carcinogen document (2), for example, placed considerable emphasis on:

- Describing the overall strengths and limitations of the data bearing on hazard identification.
- Depicting the uncertainty associated with estimated exposure levels, for example, through the use of an upper bound on exposure, a range of probable exposure values, or upper and lower confidence limits on a specific exposure estimate.
- Estimating the statistical uncertainty associated with the given risk projection, for example, through upper and lower confidence limits.
- Characterizing the variability introduced by selecting a particular low-dose extrapolation procedure, for example, by considering an envelope of risk estimates generated from a variety of plausible models.
- Evaluating the biologic variability related to the use of a particular test organism and its extrapolation to humans.

In delineating the uncertainties associated with the process of risk assessment, particularly with the quantification of risk, it is important to have a realistic perspective of mathematical modeling. Some individuals are reluctant to use or are even opposed to using mathematical modeling because of the many uncertainties associated with the process. However, it is the attendant uncertainties and not the modeling process itself that should be the primary cause for concern. Rejection of mathematical modeling out-of-hand or its use only as a last resort conflicts with current efforts to refine the risk-assessment process.

Yet, given the present status of modeling, it also seems clear that model-based estimates should not be considered by themselves without the major uncertainties associated with the generation of such estimates being characterized. This characterization should be an integral part of the estimation process and not just a caveat to the process, which is given little or no consideration. Otherwise, quantitative estimates are likely to be accorded a degree of scientific precision that may be unwarranted.

In some instances, the quality of available data may be such that mathematical modeling, although technically or mechanically possible, is scientifically questionable or unfeasible. Certainly, the lack of adequate data for modeling should never be an excuse for not taking or for postponing appropriate action to protect public health. Furthermore, since no single model is recognized as most appropriate for estimating risk, the establishment of overly detailed generic guidelines for quantitative risk estimation within the Department would seem to be questionable and, at present, the principles enunciated in the OSTP cancer document (2) probably represent the level of specificity that can be brought to bear on this question. As our ability to quantify the risk associated with exposure to toxic agents increases, however, our ability to assess the need for regulatory action and to evaluate the effectiveness of such action will also be enhanced.

SECTION 8: THE MANAGEMENT OF RISK

8.1 SCOPE AND CONSTRAINTS OF DEPARTMENTAL ACTIVITIES

Risk management has been defined in this Report as the process of integrating risk-assessment results with engineering data and social, economic, and political concerns, then weighing alternatives to select the most appropriate public health action, ranging from public education to interdiction, that will lead to reduction or elimination of the identified risk. In one sense, use of this term oversimplifies the tasks assigned to DHHS, while, at the same time, it emphasizes DHHS's operational role rather its goal of improvement of human health and well being. As an example of this, units in DHHS advise agencies with direct risk-management responsibilities (for example, ADAMHA provides advice to the Drug Enforcement Administration, NIOSH advises the Occupational Safety and Health Administration, ATSDR advises EPA, etc.). DHHS units provide useful information to facilitate decision making and optimal management of risks, which is indicative of the broad role the Department has in protecting the public health.

As noted in Subsection 6.3, risk management integrates the activities of both estimating risk and judging its acceptability. As noted in Subsection 4.2.2, the public expects local State and Federal government, as well as industry, to be involved. Congress has mandated Departmental agencies to protect human life and health and has provided guidance through the statutes that determine, in some ways rather stringently, how this is to be done. Congress through statutory language has in some instances—for example, those concerning foods, drugs, and medical devices—largely made the risk-benefit judgment. In other areas, notably those covered under the general authority of Section 301 of the Public Health Service Act, the Department has wider discretion and may choose among various nonregulatory risk-management options. Overall, however, statutory, scientific, organizational, and political constraints substantially limit the options.

For Departmental agencies with a regulatory function, like FDA and, to some extent, NIOSH, a third and often overlooked issue is involved. The questions of both risk assessment and risk acceptability require information for their resolution. If the information is inadequate, as it often is initially, the question arises as to who should supply the critical information. Frequently, the law answers the question, and it answers it differently, depending on the nature and source of the exposure. Much of the controversy over the decisions concerning toxic substances arises from difficulties in gaining agreement about who should produce the critical information and in deciding when the information is sufficient.

Another issue is the question of what substances to manage and in what priority. How this is done is a combination of scientific, legal, political, and social factors. This is the first risk-management decision, and a decision not to evaluate a chemical is, in essence, a risk-management decision. DHHS activities in risk management are often focused on risks deemed to have broad societal impact. Risks resulting from the large-scale use of chemical substances can fall into that category. The actual process of assessing the risk should remain independent of the value judgments that are necessarily associated with the broader issues of managing the risk. Insuring the quality and independence of the scientific component of risk-management decisions is vital to the public's ability to weigh properly the social and philosophical values intrinsic in such decisions.

8.2 OVERVIEW OF DEPARTMENTAL RISK-MANAGEMENT ACTIVITIES

Risk-management options can be arranged in a hierarchy of responses. This range of options includes: supplying scientific information; providing public information, education, and warnings; providing information to physicians and other health professionals; providing information to State and local officials; providing assistance to the public or to State and local authorities; promoting voluntary compliance with DHHS recommendations; making recommendations to other regulatory agencies; promulgating regulations; and, finally, using the Department's enforcement options. Different PHS agencies and centers use virtually all of these options to different degrees, depending on the nature of the threat, the amount of information available, the statutory constraints, and many other factors.

NIH—The results of NIH extramural and intramural research are widely distributed to both health professionals and the public. Moreover, the results sometimes culminate in policy statements that are intended to alter the behavior of both health professionals and the public in the direction of reducing human risk. A particularly good example of this activity is the Consensus Development Conference. These open meetings of biomedical scientists and others are held to assess the risk and benefit of various medical technologies. The program's objectives include fostering the dissemination of information on advances in the biomedical area and facilitating their adoption and appropriate use.

CDC—Three of CDC's six centers are involved in risk-management activities that deal with environmentally borne chemical risks; these include CEH, NIOSH, and, to a lesser extent, the Center for Health Promotion and Education (CHPE). CEH has responsibility for the nonoccupational environment and NIOSH, for the workplace. Although all the centers are necessarily involved in the hazard-identification and hazard-analysis parts of risk-assessment, they all go far beyond these steps and directly intervene in the community. This is managed in a way that engages public support and the cooperation of local health professionals and elected officials. An example of such activities at CDC is the lead poisoning prevention program for children. In this program, blood lead levels were determined in thousands of children with the help of local and State agencies. Children at risk were identified and their exposures reduced. Other examples are the testing and certification of respiratory protective equipment by NIOSH and the evaluation of potential health risks of substitute substances in the workplace.

ATSDR—ATSDR performs its risk management-related activities primarily through reviewing or generating relevant documentation on specific toxic waste sites, generating data on the toxic effects of chemicals, establishing a publicly accessible data base on the occurrence and distribution of disease as related to the presence of toxicants in the ambient environment, and through providing technical advice and assistance to public health agencies and health care providers involved in the detection and management of environmental contamination. To ascertain successful accomplishment of these activities, ATSDR maintains close relations with State and local public health officials and with the public. ATSDR is similar to CEH in its risk-management approach with the exception that its specific jurisdiction is over health risks from landfills and waste sites. Because ATSDR's mandate derives from the 1980 CERCLA (Superfund) legislation, risk management-related activities are closely coordinated with the Environmental Protection Agency (EPA).

FDA—Historically, FDA concentrated on eliminating unsanitary food production and preventing the marketing of deficient drugs. But in recent years the regulatory agenda has both shifted and expanded. As the result of both : 1) legislation regulating human and veterinary drugs and medical devices, and food and color additives; and 2) mounting public concern over environmental hazards, FDA increasingly is required to determine the level of risk acceptable in products that are properly manufactured and used as intended. The wider distribution of chemical products and the increased complexity of drugs and devices, coupled with the increased sensitivity of methods of chemical analysis, during the last two decades have generated new problems in evaluating the safety of ingested chemicals.

FDA's practical implementation of risk-management policy is largely directed by the governing statutory provisions for each category of substance. In the Food, Drug, and Cosmetic Act (FD&C) itself, statutory provisions describe about 17 different ways for the risk-benefit calculations to be handled. For example, in the context of evaluation of drugs, the important consideration is a favorable risk/-benefit ratio—one that considers the benefit of the therapy offered, the frequency and severity of side effects, and the availability of suitable alternatives. On the other hand, if a food or color additive has been shown to be a carcinogen, it cannot be approved regardless of its purpose, function, or value (Section 409(c)(3)). The statutes tolerate greater risk for substances of greater perceived value (traditional food), and they permit less risk for substances judged, at least at the time, as inherently unnecessary (additives), while tolerating intermediate risk for necessary or unavoidable substances (contaminants).

8.3 MAJOR ISSUES IN RISK MANAGEMENT

8.3.1 Communicating to the public the nature of the risk from toxic substances

Increasing public understanding of the Department's risk-management decisions is vital. Some of the confusion and anxiety over decisions concerning risks from chemicals may arise from the lack of communication about the probabilistic and inferential nature of the risk estimates and the reasons for the inherent uncertainties (see Sections 6 and 7). The Department should be sensitive to the need to clarify these matters in its public pronouncements, advisories, and regulations.

As noted in Subsection 6.4, the estimated risk is applicable to a whole population or to an "average" person. Many people appear to closely link such risk estimates with the highly individualized health-risk information they may obtain from their personal physicians. This misunderstanding can lead to either overreaction or underappreciation of the risks involved.

Another consideration is that, because it may be easier to grasp the magnitude of a chemical risk if it is compared with other more familiar risks, some have suggested greater use of such comparisons by DHHS. Because of the differing character of risks, however, the usefulness of comparative risk assessment can be deceptive and should be approached with care. Acceptability of risk, as described in Subsection 6.3, is strongly influenced by factors other than the magnitude of the risk. In addition to the factors described there, public acceptability of risk is also influenced by consumer preferences, by the consumer's perception of benefit, by the perception of whether things can be changed, and by the degree to which people trust the regulatory decision makers. One should be sensitive to the "context" of different magnitudes of risk in order to use comparative risk estimates effectively and accurately.

8.3.2 Appropriate identification of scientific uncertainties

Any center or agency of the Department with safety-advisory or safety-regulatory responsibilities needs accurate scientific information. The amount of such information an agency seeks from responsible manufacturers or from its own resources is itself the result of balancing the costs of obtaining the information against its anticipated usefulness. Therefore, at some point, the agency or center settles for the probability, rather than the certainty, that the risk of a product, a process, or an exposure is likely to be acceptable. Uncertainty in the science, as emphasized in both the 1983 NAS report (1) and the OSTP carcinogen document (2), is the dominant analytic difficulty in linking exposure to chemicals with chronic health effects (see also Sections 4 and 7).

Because of this difficulty and the need for timely risk-management decisions, gaps in information inevitably are filled by inference and judgment. To ensure that scientifically credible decisions are made, it is vital that such inferences and judgments be made independently of political concerns that must inevitably influence the overall risk management. It is, therefore, important to document risk assessments and scientific matters in risk management as completely as possible, fully explaining the scientific inferences that may be necessary to bridge gaps in data.

8.3.3 Peer review of risk management

Scientific peer review is widely and variously used by the units of the Department. It influences not only the gathering of scientific information, but also its interpretation, and where permitted by statutory mandate, even enters into the intervention and control phases of risk management.

Such peer review is most useful when conducted early in the process, well before the actual decision. NAS (1) has recommended that one appropriate way to foster consistency in the management of the risk from chemical carcinogens is for Federal agencies to adhere to peer-reviewed, scientifically supportable guidelines, flexibly applied on a case-by-case basis. Peer review, while desirable, may not be practical for all aspects of all risk-management decisions. Because of time constraints, it may not be logistically feasible under certain circumstances. However, peer-review activity should be encouraged by DHHS where appropriate.

8.3.4 Shared responsibilities for risk-benefit decisions

In a broad sense, "society" chooses between the perceived or known benefits and the potential risks of available new technologies. On a more practical level, the actual responsibility for assessing risks, weighing benefits, and making choices about any given class of potentially toxic substances is shared with Congress, principally, the regulatory components of DHHS, the manufacturers of regulated products, and, ultimately, the consumers and the public. An important question for some of these groups is who takes the risk and who gets the benefit. This splintering of responsibility for deciding the acceptability of risks can significantly limit any one institution's ability to perform a comprehensive risk-benefit analysis.

In addition, Congress may, at any time after DHHS has made a decision, overrule the Department's independent assessment of risk and its acceptability by revising the criteria for decision. In 1976, for example, Congress enacted the Proxmire Amendment to the FD&C Act, limiting FDA's authority to regulate the composition and labeling of foods marketed as dietary supplements. Again in 1978, Congress imposed the still current moratorium on FDA's action to ban saccharin, despite the mandate by the Delaney anti-cancer clause to enact such a ban.

8.3.5 Weighing the options

The impact on the public of a risk-management decision needs to be considered unless statutory mandates dictate otherwise. For example, it should be determined that discontinuing a common practice or banning a substance does not cause undue hardship or create a greater risk (for example, discontinuation of the chlorination of drinking water would result in epidemics). If a chemical is suggested as a substitute for another chemical, the hazard of the new chemical should be evaluated as well. Recommended actions to reduce a hazard must be technically feasible and sound. To foster the public trust, the available options and their drawbacks should be made public knowledge. The decisions made should be practical, and it must be possible to implement them. In some instances the input of the affected population needs to be incorporated into the decision-making process of risk management.

8.4 CONCLUSION

In the final analysis, risk-management decisions are made by officials who are politically accountable and who operate through procedures that permit public participation. The Department's efforts to conduct effective risk-management decisions rest on a few basic principles:

- DHHS procedures should require or stimulate the gathering of all pertinent scientific and other information about a product or activity.
- All data on which public risk-management decisions are made, including all data from studies, should be available for public examination as early as feasible.
- DHHS should seek outside expert advice and assistance when necessary.
- As far as possible, procedures designed to facilitate scientific inquiry into regulatory matters should replace formal, trial-type hearings; when legal procedures are necessary, they should be informal rather than formal.

These principles reflect a focus on and a commitment to an open decision-making process. However, an agency cannot conduct its affairs by holding a popular vote on each decision; it cannot poll the citizenry, or even that portion of the population immediately affected, before deciding whether a risk is acceptable. By seeking the views of outside persons and consulting advisors with acknowledged expertise, DHHS can, however, strengthen the legitimacy of the controversial social choices it must make.

SECTION 9: A PROBLEM-SOLVING APPROACH IN RISK MANAGEMENT

9.1 INTRODUCTION

The major challenge in risk management is to enhance public welfare through effectively managing the risks of a chemical that has toxic effects under practical conditions of use and exposure. This challenge can be addressed either compound by compound or generically. The generic approach provides a systematic framework for overcoming process-related difficulties through analysis of the risk assessment, analysis of possible options, promotion of understanding and acceptance of risk-management decisions, and evaluation of the effectiveness of the options chosen in the context of the endpoint—that is, an effective risk management decision. This approach can be termed a "problem-solving" approach to risk management. Although this differs from the formalized set of procedures usually defined as "problem solving" which have been used by regulatory agencies for some time, it emphasizes that each risk-management action, besides addressing issues in public health, can also be seen as an example of a solution to a complex problem, from which we can learn. Effective approaches to problem resolution presently are developed as a part of the everyday workings of agencies. The "problem-solving" approach identified in this section simply seeks to facilitate this process.

This "problem-solving" approach employs as many aspects of the scientific method as possible. For instance, when options are implemented, emphasis is placed on evaluating the effectiveness of the option selected. Since this "tests" the solution, it provides data that will lead to an overall improvement in the risk-assessment/management process. Part of this approach is also the sharing of techniques and methods among agencies, much like communicating results to a scientific public, a process done informally now.

Overall, risk assessment and risk management can be seen as parts of a dynamic process in which government acts directly to resolve uncertainties, to increase public participation, and to develop options that enhance public welfare. The approach continues and expands efforts already begun toward assuring risk managers and the public that as much expertise as possible has been brought to bear in evaluating all reasonable options and choosing the best solution.

Historically, various governmental units involved in risk assessment and risk management have resolved problems when faced with individual concerns. For example, in 1980, a decision was made to mandate costly changes, suggested by chemical industry representatives, in the design of railroad tank cars that transport chemicals. These changes have greatly reduced the risk of toxic exposure. The direct cost benefits of the decision for industry have been reductions in insurance premiums for chemical transport and in the possibilities of costly litigation. Thus, compliance with a decision important to the public health was maximized. This action is an example of one agency's creative method, and the "problem solving" approach attempts to facilitate creative solutions such as these.

9.2 ANALYSIS OF THE RISK ASSESSMENT

In the analysis of a risk assessment, questions may arise when the endpoint of an effective risk management decision is considered, for example: 1) what is the nature of the uncertainty in the assessment; and 2) how does this assessment compare with others.

1) Uncertainties in risk assessments (see Section 7). Uncertainties in a risk assessment, if not addressed, may lead to a lack of confidence in the risk-management decision resulting from the assessment. To prevent this, the authors of a risk assessment should, when feasible, identify major sources of uncertainty in the assessment. This is not a simple task, since the amount of information needed to address different assumptions usually varies from compound to compound, on a case-by-case basis. Because of unique expertise and familiarity with the uncertainty involved in the risk assessment of a particular chemical, it would be useful, when practical, for a risk assessor to point out areas that could profit from specific research.

2) Comparison with other risk assessments. Different government agencies sometimes do risk assessments on the same chemical because different aspects of the chemical's use fall under different mandates. Comparing the different risk assessments as part of "reviewing the literature" places the assessment of a chemical in context. Since the public will also compare these different assessments, the reasons for any differences in assessments on the same chemical should be made evident. This would help explain the risk-management decisions to the public. Of course, although different assumptions may account for this variation, each assessment may be equally valid. It would also be useful—to prevent potential problems—if the discussion could suggest how and if any differences could be addressed.

9.3 ANALYSIS OF POSSIBLE OPTIONS

When analyzing the possible options in a risk-management decision, it is important to keep in mind the goals of 1) enhancing the public welfare, and 2) maximizing the effectiveness of the decision. Estimating the costs of an option and its possible benefits is an important part of deciding how to manage risk effectively. This estimation increases public confidence in risk-management decisions when it is clearly demonstrated that a wide range of options was considered and that those with the least risk and most benefit (under realistic legal and technological constraints) were chosen. Discussions of benefits usually focus on the economic and consumer-oriented aspects, but health benefits may also be associated with substances that may be toxic. The health costs associated with different risk-management options, when applicable, should be included. The most striking example of this is the risk associated with therapeutic drugs, in which the benefits of treatment and the consequences of nontreatment are well appreciated. Another example concerns the chlorination of water supplies. Although the chlorine reacts with organic compounds in the water to produce toxic substances, the health benefits of its bactericidal action are important factors in its continued use.

Risk-management decisions can be used as an opportunity for government expertise to attempt to protect the public health and resolve problems in a manner which minimizes losses and maximizes gains. This approach strives to achieve a solution in which nobody loses and everybody stands to gain. As with all "perfect" goals, practical factors, such as technological and legislative constraints must be considered, and a compromise is the usual result. However, such solutions enhance the public welfare, within the boundaries of conditions at the time of the decision. Enhancing the public welfare has been an important part of agency efforts; however, it is useful to make it clear that an attempt has been made to do this, so that each element in the population will feel that its needs have been considered. Thus, disputes are less likely to arise. It should be appreciated that the various governmental units involved in risk management have already implemented aspects of this creative approach to risk management in their daily operations, for example, the sensitivity-of-method approach in FDA, which removes a barrier to the development of ever more sensitive analytical techniques without compromising public health. Some examples of options are:

1) **DHHS regulatory action.** The benefits and costs of this option should continue to be evaluated, with estimates of compliance and suggestions of methods to maximize and evaluate compliance clearly identified. The factors involved in the full range of regulatory responses (the hierarchy of responses discussed in Section 8) should continue to be made explicit, with the reasons made clear for choosing a response (or range of responses).
2) **Regulation by other governmental units.** The role that State, local, and other Federal units play in regulating substances should be highlighted. Specific considerations associated with a particular chemical, such as the role of other risk assessments and risk-management decisions about the chemical, should be explicitly stated, with the goal of expediting communication and interaction between all levels of governmental agencies.
3) **Risk reduction by technologic means.** Strategies to reduce risks of toxicity associated with a chemical are sometimes feasible, despite technical problems and the legal confines of the enabling statutes. Examples include detoxification of a material, filtration, containment, or use of available alternative substances. Clear expression of technologic solutions, when available, would continue to emphasize the government's role in protecting public health without being unreasonably restrictive.

4) **Public education.** Public education is often used as a tool in protecting the public health, but the public's understanding of the complex issues in risk assessment and risk management has not kept up with its interest in the issues. In any document, it would be very useful to state the risks, benefits, options, and important factors (such as statutory mandates) entering into the risk-management decision in a special section in clear, straightforward language aimed at the layman. In this educational process, risk managers should continue to reach out to the public. Making complicated issues clear is not easy, but it is important for effective use of information by the public. In addition, the effectiveness of public education strategies should continue to be periodically evaluated and modified to maximize effectiveness.
5) **Voluntary actions by the private sector.** These actions are an important part of creating confidence in and compliance with risk-management decisions. As part of an effective risk-management strategy, regulatory units have for years suggested compliance methods and standards to be adopted voluntarily. Explicit consideration—covering attendant risks, benefits, and expected compliance—of the alternatives that require a minimal amount of governmental intervention and resources would stimulate use of voluntary action.
6) **Professional societies.** Professional societies have a long history of public service and an interest in public health. Cooperating with them refines the science in risk assessment and risk management and also stimulates confidence in and acceptance of risk-management decisions. These societies are a valuable resource for reviewing documents, assisting in clarifying consensus positions, promoting acceptance by scientific communities, and for other purposes. This resource has been tapped in many instances, but more formal consideration of this option would promote its use.
7) **Risk-management research.** Lack of scientific knowledge creates problems in choosing a course of action, and it can cause lack of confidence in the final decision. Since risk managers and risk-management scientists have a special appreciation of the problems involved in the risk management of a particular chemical, they can and should be used as much as possible to suggest research that may resolve uncertainties. Here, as for risk assessment, research should be integrated with broader efforts, in this case to address the uncertainty in risk management as a whole. Practical suggestions for research that address the significant sources of uncertainty in risk management should be formalized as part of many risk-assessment documents. Again, the possibility of research should not be a reason to postpone action, but an important part of removing the uncertainty.

9.4 PROMOTION OF UNDERSTANDING AND ACCEPTANCE OF RISK—MANAGEMENT DECISIONS

To maximize public support of and compliance with a risk-management measure, it is important to get affected parties to participate in and understand the major aspects of decisions. Dissemination of information about the factors in the decision to other health-related agencies and to the affected parties has been adopted by many units to present the risk-management decisions for public comment. Understanding and acceptance can be encouraged by expanding our efforts to inform all interested health agencies and other State and local agencies. This network includes primary care physicians, who will be the front line in addressing much of the public's concern about health and toxic exposure. The risk-management decision, when clearly stated, is an effective and useful tool for local agencies, medical societies, interested local organizations, and individuals.

9.5 EVALUATION OF EFFECTIVENESS OF OPTIONS

"Testing" the results of a decision is an important part of a decision-making process that solves problems. Information on the efficacy of options has a very important role in improving the generic process of selecting options. Although different governmental units involved in risk-management activities evaluate some consequences of their risk assessment and risk-management activities, it has not been a general policy to formalize a procedure to test how effective the selected option was. When practical, the effectiveness and costs of a risk-management decision should be evaluated through follow-up in order to provide a historical record of corrective options. Further, if conditions change or if the follow-up shows that a solution is ineffective, the risk manager may decide to alter the decision through subsequent action. Such information would be an integral part of an ongoing corrective risk-management process in a formalized means as opposed to depending exclusively on institutionalized memory. How each unit accomplishes this depends on the factors specific to that unit. The units that have engaged in this activity have, however, been very creative in using available resources and tailoring procedures to the units' particular needs.

9.6 CONCLUSION

Parts of this "problem-solving" approach to risk management have been suggested or implied elsewhere in other forms. Other parts have been done in different degrees by different units at different times. Presented here is a synopsis of a framework for analysing risk-management decision processes and an illustration of some of the difficulties to be overcome in the context of the endpoint to be achieved. Using this integrated approach, DHHS can continue to address the problems in risk assessment and risk management in a comprehensive fashion while facilitating the process further. Because of its broad, important role in basic and applied research, as well as its needs, DHHS should take steps to more clearly state its ongoing activities in this area and coordinate its approach.

SECTION 10: RECOMMENDATIONS

This section consists of five subsections. The first three each contain a general recommendation, discussed in a narrative form. Subsection 10.4 contains other, more specific, administrative recommendations listed without narrative. Subsection 10.5 contains suggestions for research that would improve the ability to deal with the complex issues of risk assessment and risk management, again listed without narrative. These recommendations derive from needs stated in previous sections of the Report. It should also be noted, however, that additional recommendations are made throughout this Report.

10.1 AGENCY POLICY ON THE CONDUCT OF RISK ASSESSMENTS

Each agency should be encouraged to develop a policy on the practice of risk assessment within that agency. Among the issues that might be addressed are the circumstances under which risk assessments are initiated within the agency, reflecting, for example, statutory mandates, agency mission, and so on.

When a policy is being developed, consideration should be given to such sources as recent task force reports, concensus documents that have addressed this issue, such as the NAS report (1), the NCAB/NCI report (14), and the OSTP document (2). Attention should also be directed to the various issues discussed in Section 7 of this Report, including a delineation of major assumptions and a characterization of uncertainity.

10.2 SCIENTIFIC PEER REVIEW OF RISK ASSESSMENT AND RISK MANAGEMENT WITH PUBLIC PARTICIPATION

Scientific peer review remains fundamental to good research: basic, developmental, and applied. Peer review provides indispensable, objective criticism and public exposure of new findings and ideas and maintains a critical oversight on the quality of science. This need was clearly recognized in the NCAB/NCI report on risk assessment (14) and by the NAS report (1). In particular, the NAS report (page 151) urged "continuing review and modification of risk assessment procedures...," and in 2 of 10 recommendations offers specific advice to assure that the peer-review process remains readily and actively available to the public. If public trust in science-based governmental decisions is to be gained and maintained, all research conducted and supported by the government (and in particular data used and conclusions made in the risk-assessment/risk-management process) should have a system of unbiased and balanced peer review.

Agencies should review their peer-review processes in light of the need to ensure public participation in risk assessments and, where possible, risk-management actions. The data resulting from long-term toxicology and carcinogenesis studies in laboratory animals exposed to chemicals are most often the primary information used both to identify potential hazards to humans and to initiate the formal risk-assessment process. Governmental agencies that generate, interpret, and evaluate these data or use these results in risk assessments should be urged to share this information and the process not only with other Federal agencies needing those data but with the public as well as soon as feasible. This is not an easy task. The issues are complicated ones, with much potential for misunderstanding. However, it is an important part of how DHHS does business, and has been a goal for the various agencies in the Department for some time. Given the different research and regulatory missions of the agencies generating the necessary data for use in risk evaluations and the separate missions of the agencies formulating risk assessments, each group may adopt a system of public peer review oriented to suit best its stated goals.

10.3 COMMUNICATION AMONG DHHS AGENCIES

Continued information exchanges and active communication among agencies involved in the multifaceted risk-assessment/risk-management process augurs well for better use of available resources and for sharing vital knowledge. Whereas much communication occurs among individuals involved in this scientific discipline, more attention should be directed toward making sure that the activities surrounding the various stages of the risk-assessment process become better known among those at different agencies who are involved in the multiple levels of these complex processes. A more formal system of structured communication would be advantageous in general and beneficial to each agency. Communication and active interaction with other agencies outside the Department and in the private sector should be pursued. Existing and relevant interagency activities already functioning within the Department (Executive Committee, CCERP; CCERP; NTP; etc.) should be explored to fill this need. For instance, the Executive Committee, CCERP, should explore mechanisms in PHS to insure coordination in DHHS risk assessment and risk-management activities. Risk assessors, risk managers and experimentalists should communicate.

Another key area that would benefit from increased attention centers on the extended awareness and wider distribution of the end results (documents, reports, risk assessments, position papers, publications) of the risk-assessment process. This could be accomplished by establishing a central focus or procedure within each agency for information exchange and document distribution. Integral to the process of better informing the public are educational and community outreach programs that explain more fully and pragmatically the risks, risk assessments, and risk-management (control-strategy) decisions.

10.4 OTHER ADMINISTRATIVE RECOMMENDATIONS

In addition to the general recommendations in the previous three subsections, others of an administrative nature are:

1) DHHS research efforts that relate to risk assessment and risk management should be catalogued periodically and comprehensively. The catalogue should be distributed to interested government agencies and made available to the public. This effort might benefit if coordinated with the the NTP *Review of Current DHHS, EPA, and DOE Research Related to Toxicology.*
2) Opportunities for sharing staff expertise, available information data bases, agency experience, and relevant topical reports should be encouraged and made more widely known within the Department. Continued development of agency expertise by seminars, training courses, and interagency workshops is recommended.
3) The Executive Committee, Committee to Coordinate Environmental and Related Programs (CCERP), should explore mechanisms within PHS to ensure coordination in DHHS risk-assessment and risk-management activities.
4) The development of formal training programs in risk assessment relevant to public health should be encouraged.
5) Increased efforts should be given to the development of record linkages in Federal agencies that may disclose health effects in human populations in association with particular exposures (as recommended by CCERP in 1983). There is increased need to improve access to such systems while safeguarding the rights of individuals.

10.5 RESEARCH NEEDS

Some of the areas in which increased knowledge would improve the ability to deal with the complex issues of risk assessment and risk management are listed below. The outline provides an overview that is by no means all-inclusive. This list should not be considered to represent entirely novel ideas, since research in these areas may already be in progress. Further, some of the recommendations may have already been made in the context of other reviews addressing different areas of environmental and public health (for example, ref. 15)

Recommendations for research in general toxicology useful for risk assessment are:

1) Enhance research on interaction between toxic chemicals and genetically susceptible hosts (for example, modulation of the gene expression);
2) Enhance development and improvement of in-vitro and in-vivo predictive toxicology systems;
3) Enhance development and improvement of biomarkers as early indices of exposure and as early diagnostic sentinels, with specificity and predictability for health outcomes of individuals;
4) Encourage experimental research clarifying the relationship of animal variables, such as weight and dietary composition, and the molecular basis of toxicologic endpoints;
5) Encourage development of an interspecies comparison in toxicologic research, to understand better and predict qualitative and quantitative differences in the response to toxic chemicals.

Suggestions for research needs that would improve methodology in the estimation and projection of risk are:

1) Encourage development, validation (when possible), and improvement of mechanistically based mathematical models, particularly for noncancer health outcomes.
2) Encourage the validation of assumptions used in risk assessment approaches and modeling (e.g., assumptions about interspecies differences, average dose, and low-dose extrapolation).
3) Encourage development of exposure assessment and dose-response assessment aimed at dealing with the prediction of the risk from human exposure to multiple chemicals via multiple media and routes, at varying levels, for less than a lifetime.

Suggestions for research in epidemiology that would be useful for risk assessment are:

1) Encourage the conduct of epidemiologic studies aimed at testing the accuracy of risk projections derived from animal data and modeling.
2) Ensure that exposure and disease registries are established only when scientifically justified.
3) Encourage the conduct of epidemiologic studies that incorporate biochemical and molecular probes to clarify exposures, precursor states, and mechanisms of action.
4) Encourage the conduct of epidemiologic studies that evaluate interactions between toxic chemicals, life-style practices, and host susceptibility.

SECTION 11: REFERENCES

1. Committee on the Institutional Means for Assessment of Risks to Public Health, National Research Council. Risk Assessment in the Federal Government: Managing the Process. Washington, D.C.: National Academy Press, 1983.
2. Interagency Staff Group on Chemical Carcinogenesis. Chemical Carcinogens: A Review of the Science and Its Associated Principles. Washington, D.C.: U.S. Office of Science and Technology Policy, 1984. Federal Register 1985; 50:10372-10442.
3. Lowrance WW. The nature of risk. In: Schwing RC, Albers WA, Jr., eds. Societal Risk Assessment. New York: Plenum Press, 1980: 5-16.
4. Doull J, Klaassen CD, Amdur MO, eds. Toxicology: The Basic Science of Poisons, 2nd ed. New York: Macmillan, 1980.
5. Rom WM. Environmental and Occupational Medicine. Boston: Little, Brown, 1983.
6. Mausner JS, Kramer S. Epidemiology: An Introductory Text. Philadelphia: W. B. Saunders, 1985.
7. National Academy of Sciences. Drinking Water and Health, vols. 1-5. Washington, D.C.: National Academy Press, 1977, 1980.
8. Slovic P, Fischhoff B, Lichenstein S. Rating the risks. Environment 1979; 21: 14-39.
9. Slovic P, Fischhoff B, Lichenstein S. Informing people about risk. In: Morris L, Mazis M, Barofsky B, eds. Product Labeling and Health Risks. Cold Spring Harbor, N.Y.: Banbury, 1980: 165-181.
10. Slovic P, Fischhoff B, Lichenstein S. Why study risk perception? Risk Analysis 1982; 2: 83-93.
11. Morgan MG. Probing the question of technology-induced risk. IEEE Spectrum 1981 (November): 58-64.
12. Morgan MG. Choosing and managing technology-induced risk. IEEE Spectrum 1981 (December): 53-60.
13. Committee on Chemical Environmental Mutagens, National Research Council. Identifying and Estimating the Genetic Impact of Chemical Mutagens. Washington, D.C.: National Academy Press, 1982.
14. Samuels SW, Adamson RH. Quantitative Risk Assessment: Report of the Subcommittee on Environmental Carcinogenesis, National Cancer Advisory Board. JNCI, April 1985.
15. Third Task Force for Research Planning in Environmental Health Science. Human Health in the Environment: Some Research Needs: A Report to the Committee on Appropriations, U. S. House of Representatives, December 1984. (Publication No. NIH 85-127) In press.

SECTION 12: APPENDIX

12.1 SECRETARY HECKLER'S MEMORANDUM

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

January 25, 2985

MEMORANDUM TO: Chairman, Executive Committee, CCERP
SUBJECT: Risk Management of Toxic Substances

Several items have required my attention recently which indicate that our Department may not have a clearly articulated and well implemented policy on risk assessment and management for toxic substances. These items include worker notification policy; the National Toxicology Program Report on Carcinogens; and the proposed reorganization of the Agency for Toxic Substances and Disease Registry.

There is no question that we have done an excellent job in problem identification which is of course an important first step in any program. I believe that this work should continue. I also believe that the public now expects and deserves the logical next phase which is problem resolution. This phase must go beyond the simplistic solution of banning production or use of all toxic but useful substances in order to create a risk free environment.

In fact, this phase of risk assessment and management will be far harder than the problem identification phase. For example, some issues present an estimate of risk that varies by several orders of magnitude depending on whether one accepts the estimates of consumer groups or industry. A natural inclination is to pick an estimate somewhere in the middle. Unfortunately, this kind of process leaves the decision-maker with what I consider to be more doubt than is ncecessary as to the veracity of a decision.

For my own part, as of now, for decisions I must make in the future on issues of risk management, I will expect an analysis that includes:

— A discussion of the assumptions that were necessary beyond the quantitative assessment of risk. For example, what was assumed about the extrapolation of risk from small animal studies to humans? What are the assumptions about amount of ingestion over time, etc.

— A discussion of possible alternative substances available or, if possible, methods by which a substance may be rendered safe or controlled in such a way as to avoid harmful exposure.

— A discussion of alternative non-Federal sources of risk management. For example, do State and local governments or private associations have jurisdiction?

Finally, while the description and reduction of risk are not likely ever to be reduced to simple formula calculations, I believe that it is time for us to do a thorough analysis of all of our programs in toxicology research, scientific risk assessment and risk management with several goals:

— defining a single philosophy of risk and what we should do about it;

— describing the most common assumptions upon which risk assessment is based;

— developing in concept a problem solving approach toward risk management.

I realize that this will not be an easy task, but I believe that timing is critical. As you know, the Interagency Risk Management Council has been elevated to Cabinet Council status and this Department will be the lead player in this effort. I will be looking to you and your Executive Committee to provide advice to me for this Council effort. While the membership on the working groups of this Council has not been fixed as yet, I believe we need to get a head start by at least having HHS well prepared from a general policy standpoint. Therefore, I request the receipt of your analysis 90 days from today.

Margaret M. Heckler

Margaret M. Heckler
Secretary

12.2 SURVEY QUESTIONNAIRE SENT TO PHS AGENCIES

REQUEST FOR INFORMATION
for the
TASK FORCE ON RISK ASSESSMENT

INTRODUCTION

The purpose of this questionnaire is to obtain information on DHHS activities related to risk assessment and risk management of toxic substances. The information furnished by each agency will be used by the Executive Committee, CCERP, to reply to a request from the Secretary, DHHS, who asked for scientific input into questions concerning risk analysis. We see this task as an important one, and we ask for your assistance.

Definitions —

For a number of reasons, including historical ones, the terms used in reference to risk have acquired a variety of different meanings. We have therefore provided a glossary of terms concerning risk assessment and management for use in answering this questionnaire. Please understand that the definitions in the glossary have been purposely kept brief to facilitate their usage. They should be construed as working definitions, and are not intended to be exhaustive in their construction. The terms in the glossary should be understood before attempting to answer the questionnaire.

Some of the information sought on toxicology resources is similar to that requested for the Annual Plan of the National Toxicology Program (NTP). However, there are some signficant differences between our needs and those of NTP. Therefore, the information provided here will not be redundant with that provided to the NTP.

Some of the questions in this questionnaire will require you to respond on separate sheets of paper. When you do, please identify each attachment by Part and Question number. Also, when we ask for estimates of funds, we mean total funds (i.e., include personnel costs) for FY 1985.

PART 1 — DEFINITIONS

1) Can you accept the working definitions given in the attached glossary? (Note, they were purposely kept brief.) Y N

2) If no, please elaborate what you would change and how.

PART 2 — AGENCY'S MISSION/MANDATE

1) Please attach a concise statement of your mission statement and legislative mandate, and what role you feel that risk analysis plays in accomplishing those aims.

PART 3 — PHILOSOPHY OF RISK

1) Please attach a concise statement of what you feel is the philosophy (or philosophies if more than one) of risk that are utilized in your agency.

PART 4 — RISK ANALYSIS

1) Does your agency conduct, review, or otherwise participate in the formation of risk assessments? Y N

2) How many risk assessments does your agency conduct, review, or otherwise participate in per year? ________

3) What is your agency's estimate of the resources devoted to these assessments per year?
$_______ FTE's ______

4) How many quantitative risk assessments conducted each year incorporate all four elements (see the glossary) of risk assessment?

5) What is your agency's estimate of the resources devoted to these assessments per year?
$_______ FTE's ______

6) Is your agency involved with state and/or local agencies in risk analysis? Y N

7) If yes, please attach a concise statement of the scope of this activity.

8) Do you coordinate your risk-analysis activities with other Federal governmental units?
Y N

9) If so, please attach a concise statement of how.

10) Does your agency conduct some form of scientific peer review and/or public review of risk assessments and/or risk-management plans? Y N

11) If yes, please attach a description of your agency's process.

12) Does the agency have a written policy for conduct of a risk assessment? Y N
If so, please attach a copy of the guidelines to the questionnaire.

13) Is your agency involved in risk management? Y N

14) If so, please attach a concise statement of how.

PART 5 — RESOURCES INVOLVED IN RISK ANALYSIS

Please indicate for each area your estimate of how many resources are allocated. If a study's primary purpose is to add to the general body of scientific knowledge, then list it in Part A. If the intent is to add to our knowledge of the toxicity of a specific compound, then list its resources under Part B.

A. Research in Toxicology

1) Basic Research — Mechanistic studies that provide explanations of how damage occurs from exposure to toxic substances in biological systems.
$_______ FTE's ______

2) Applied research — Studies which are not mechanistic, not applied toward risk analysis, but which add to the body of toxicological knowledge and which may ultimately be useful in risk analysis.
$_______ FTE's ______

3) Research Applied to Risk Analysis —
a. Risk Assessment

1) Research primarily designed to evaluate and test the validity and predictions of the assumptions used in the different steps in risk assessment and risk analysis (including biological and statistical research). $_______ FTE's ______

2) Research into assessing risks from mixtures of agents. $_______ FTE's ______

b. Risk Management

1) Research on the evaluation and development of alternative methods in risk management (all areas). $________FTE's______

Specific areas—
Detoxification $________FTE's______
Substitute materials $________FTE's______

2) Research into the evaluation and development of methods of assessing the effectiveness of risk-management strategies $________FTE's______

c. Other

1) Other research you think is applied directly to questions in risk assessment and risk management (please categorize and denote resources). Exclude the studies included in Part B.

B. Generation and Application of Scientific Data in Risk Analysis

1) Hazard Identification — What resources are devoted to the generation of data for, or are utilized in, risk analysis in the following areas?

a) Epidemiology studies $________FTE's______

b) Animal studies $________FTE's______

c) Short-term studies $________FTE's______

d) Comparative structure-action studies of hazardous molecules $________FTE's______

e) Health assessment (e.g., disease registries, health surveys, medical screening, case reports, and surveillance) $________FTE's______

f) Other (please categorize and denote resources).

2) Dose-response assessment — What resources are allocated to the following areas that generate data for, or are utilized in, dose-response assessment?

a) Epidemiology studies $________FTE's______

b) Animal studies $________FTE's______

c) Biometric models, statistics and extrapolation $________FTE's______

d) Other (please categorize and denote resources).

3) Exposure assessment — What resources are allocated to the following areas that generate data for, or are utilized in, exposure assessment?

a) Analysis of exposure in human populations $________FTE's______

b) Surveys (e.g., environmental or occupational monitoring) $________FTE's______

c) Exposure estimation using biomarkers $________FTE's______

d) Analytical methods application $________FTE's______

e) Measurements and models of transport and exposure $________ FTE's______

f) Other (please categorize and denote resources).

4) Risk Characterization — What resources are allocated to studies which generate data for, or are utilized in, risk assessments in the following areas?

a) Preparation of risk estimates and the documents to be used by decision makers. $________ FTE's______

b) Integrative and evaluative studies which specify uncertainties and how to interpret them. $________ FTE's______

c) Other (please categorize and denote resources).

5) Risk Management — What resources are allocated to studies which generate data for, or are utilized in, risk management in the following areas?

a) Administrative alternatives for the management of identified risks. $________ FTE's______

b) Control technologies (all areas) $________ FTE's______

Specific areas —
Detoxification $________ FTE's______
Substitute materials $________ FTE's______

c) Cost/benefit analyses $________ FTE's______

d) Other (please categorize and denote resources).

6) What resources are allocated to studies which generate data for, or are utilized in, evaluating the effects of risk management strategies? $________ FTE's______

PART 6 — OTHER ACTIVITIES RELATED TO RISK MANAGEMENT

What resources are allocated to the following areas to support risk-management activities?

a) Formation of options or administrative alternatives for the management of identified risks. $________ FTE's______

b) Evaluation and utilization of control technologies (all areas) $________ FTE's______

Specific areas
Detoxification $________ FTE's______
Substitute materials $________ FTE's______

c) Cost/benefit analyses $________ FTE's______

d) Evaluation of the effects of risk management strategies? $________ FTE's______

e) Other (please categorize and denote resources).

PART 7 — FUTURE RESEARCH AREAS

1) Do you feel there are any research areas that would be very fruitful to explore in improving the science that enters into risk analysis? Please list.

PART 8 — LIST OF PROJECTS

Please provide a list of titles of experiments and/or projects relevant to risk analysis conducted by your agency. These are the projects/experiments that were used to derive the estimation of resources asked for in Parts 5 and 6. Please separate the projects/experiments into the categories found in Parts 5 and 6. If this would delay the response to the questionnaire, please send in the rest of the questionnaire as soon as possible and submit Part 8 within the next week.

GLOSSARY OF TERMS

RISK — The possibility or probability of an adverse health effect as a result of exposure to a hazardous substance.

RISK ASSESSMENT — The use of available information to evaluate and estimate exposure to a substance and its consequent adverse health effects. Risk assessment consists of the following four elements:

HAZARD IDENTIFICATION — The qualitative evaluation of available information on a substance's ability to produce toxic effects and the relevance of this information to humans.

EXPOSURE ASSESSMENT — The types (routes and media), magnitudes, and durations of actual anticipated exposures, and doses when known;and, when appropriate, the number of individuals who are likely to be exposed.

DOSE-RESPONSE ASSESSMENT — The process of estimating the relation between the dose of a substance and the incidence of an adverse health effect.

RISK CHARACTERIZATION — The process of estimating the incidence of a health effect under the various conditions of human exposure, including a characterization of the uncertainties involved.

RISK MANAGEMENT — The process of integrating risk-assessment results, engineering data, and social, economic, and political concerns, then weighing alternatives in order to select the most appropriate public health action that will lead to reduction or elimination of the risk identified.

RISK ANALYSIS — The process that combines risk assessment and risk management.

Appendix 7

LEGISLATIVE AUTHORITIES

- Public Health Service Act
  - Section 222 (U.S.C. 217a)
  - Section 301 (42 U.S.C. 242b)
  - Section 305 (42 U.S.C. 242c)
  - Section 308 (42 U.S.C. 242m)
  - Sections 400-409 (42 U.S.C. 281-286e)
  - Sections 411-419B (42 U.S.C. 287)
  - Section 474 (42 U.S.C. 2891-3)
  - Section 505 (42 U.S.C. 290aa-4)
  - Section 510 (42 U.S.C. 290bb)
  - Section 515 (42 U.S.C. 290cc)
- Federal Food, Drug, and Cosmetic Act
  - Section 201 (21 U.S.C. 321)
  - Section 402 (21 U.S.C. 342)
  - Section 409 (21 U.S.C. 348)
  - Section 512 (21 U.S.C. 360b)
  - Section 601 (21 U.S.C. 361)
- Controlled Substances Act
  - Section 201 (21 U.S.C. 811)
  - Section 305 (21 U.S.C. 825)
- Federal Cigarette Labelling and Advertising Act (15 U.S.C. 1331)
- Comprehensive Environmental Response, Compensation, and Liability Act (Superfund)
  - Section 102 (42 U.S.C. 9602)
  - Section 104 (42 U.S.C. 9604)
- Occupational Safety and Health Act (29 U.S.C. 651 et seq.)
- Mine Safety and Health Act (30 U.S.C. 801 et. seq.)
- Resources Conservation and Recovery Act (42 U.S.C. 6901 et. seq.)

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